The New England
Journal of Medicine

VOLUME 214 MAY 28, 1936 NUMBER 22

PROTAMINE INSULIN

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INTRODUCTION. Eleven year old B. W. showed 10 per cent of urinary sugar upon the morning following the discovery of his diabetes and began the use of protamine insulin forthwith. (Figure 1.) Thirty units were given before breakfast on the first day, 50 units on the second, third and fourth and upon the fifth day, the urine was sugar-free although the patient had received in the previous twenty-four hours 210 grams of carbohydrate and 1900 calories. He had no reactions and eleven days later while at home was sugar-free with a normal blood sugar. By that time his insulin had been reduced to 24 units before breakfast. It is true he was a fresh case and a child, but contrast this experience with the inauguration of treatment with former methods.

Mrs. S., a nurse thirty-six years old, so crippled with rheumatoid arthritis that exercise was impossible in the treatment of her diabetes of one year's duration, weighed eighty-four pounds in July, 1935. To control her diabetes she required insulin in enormous amounts, given in four to six doses daily for six months. At one time she took as high as 530 units a day. Since January she has shown improvement, her weight has risen to 117¼ pounds and the insulin was decreased to 240 units administered before meals and on retiring. Upon January 23 she began protamine insulin and now in April her diabetes is equally well controlled with insulin once daily, 120 units of the old and 120 units of the new. (Figure 2.)

R.'s parents told me (E. P. J.) that since her severe reaction ten years ago they had not dared to let her sleep alone. This last autumn, the week after entrance to a college in Boston while at lunch with her mother at a restaurant, she had a reaction so violent that it was necessary to call an ambulance and remove her to a hospital. Immediately she began protamine insulin and is now taking 40-0-thirty-six.* Her mother says, "Since R. commenced protamine insulin she has had no reactions. She sleeps alone. You cannot tell, Dr. Joslin, what protamine insulin means to her father and me."

DESCRIPTION OF PATIENTS. All told, we have given protamine insulin since last August to more than 100 diabetics, but only the cases studied before April 1 are summarized in this report. Of these ninety-one patients, forty-six were males. All began it in the hospital. Their ages ranged between four and seventy-six years, thirteen being children fifteen years old or less, and the duration of the diabetes a few days to twenty-eight years. Sixty-six patients continue to take it, and the great majority of these are using it in their homes. No patient who began it has died, developed diabetic coma, or acidosis, or, as a matter of fact, *de novo* any complication common to diabetics such as lesions of the legs or carbuncles. This is not particularly strange, because the patients were selected for intelligence and reliability. One patient of eight years' duration with reactions of considerable intensity in the past has developed what at first we thought was neuritis, but probably is proving to be multiple sclerosis. However, it is our impression that the sixty-six patients now taking protamine insulin alone or in conjunction with old insulin live far more comfortably, more safely than before and with less inconvenience to themselves or their families and that they can take a somewhat wider range of carbohydrate in the diet without showing an increase in glycosuria. We are convinced, as previously reported,[1, 2, 3] that protamine insulin represents a great advance in diabetic therapy.

TABLE 1

NINETY-ONE DIABETICS TREATED WITH PROTAMINE INSULIN

Age by Decades	Number of Cases	Average Duration of Diabetes Yrs.
0-9	6	2.9
10-19	40	6.7
20-29	7	11.3
30-39	8	8.6
40-49	13	10.0
50-59	8	6.2
60-69	6	12.5
70-79	3	14.0

In an estimation of the value of protamine insulin one is forced at the moment to depend upon immediate results such as prolongation of the action of insulin and freedom from reactions, but beneficial as these are, we consider them to be insignificant in comparison with the better control of the diabetes which it makes practical. Formerly a diabetic could maintain a reasonably normal blood sugar for one-half,

*40 is the morning dose of old insulin.
0 no insulin at noon.
Thirty-six units of protamine insulin.

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two-thirds, or three-quarters of the twenty-four hours, but consider what this signified if applied to the course of his diabetes throughout twenty years—the average duration of diabetes with onset in 1936. It would mean that for one-half to one-quarter of this period, namely, ten to five years he would be living with an abnormal blood sugar with all its implications. And it is this long range view of the diabetic problem which is ultimately the more important.

THE HAGEDORN ERA. Whereas the Banting Era made possible the conquest of coma, the Hagedorn Era makes possible the approximation of the physiological processes of the diabetic so nearly to normal that arteriosclerosis should cease to be his distinctive enemy. Protamine insulin has broken the spell of content which the original insulin induced. Now we know improvement in insulin is possible. These are the chief reasons that for ourselves we think it only fair and a just due to the Copenhagen investigator to name this present era the Hagedorn Era.[1]

We will next present the technique we have employed in the administration of protamine insulin, the dosage, the diets, the untoward effects such as reactions, hypoglycemic or allergic, the apparent lack of control of the disease in the inauguration of treatment and the reasons why having begun protamine insulin certain patients omitted it. Finally, we will state as best we can the indications for its use and the suggestions we have for its employment with new diabetics and for the transfer to new insulin of diabetics already under treatment with old insulin.

GENERAL TECHNIQUE. The diabetic patient can be treated entirely with protamine insulin or with combinations of old and protamine insulin. With fresh cases of diabetes we have been greatly impressed with the effectiveness of the use of protamine insulin exclusively and believe that it is desirable to follow this up intensively. When both old and protamine insulin are employed our most consistent results have been secured by following the original suggestion of Hagedorn[3] of giving old insulin in the morning and protamine insulin before the evening meal. The cases we started upon this plan nine months ago have done remarkably well and so well that they furnish a standard for comparison with other methods.

A small number of patients have been given both old and new insulin before breakfast and old and new insulin before the evening meal and a group of these have found this method so satisfactory that we hesitate to change them to other types of treatment. Knowing in advance the results obtained by Campbell, Best and Wilder[4, 5] with simple doses of old and protamine insulin given separately before breakfast, we have tested this method more especially in the last few weeks and it has worked well.

DETAILS OF ADMINISTRATION. The present protamine insulin compound in use in this country is obtained, as in Copenhagen, by mixing two solutions which come in separate bottles. In the first is a solution containing standard insulin of U-50 strength. In the smaller bottle accompanying the larger one in the same package is a solution containing protamine derived from fish sperm. When 1 cc. of the protamine solution is injected into the bottle containing the U-50 insulin, a cloudy, milky mixture is formed which is really a suspension of the finely divided and almost insoluble protamine insulin compound. This compound has its point of minimum solubility at pH 7.3, or at about the reaction of blood serum. This cloudy suspension is injected.

The effectiveness of the new protamine insulin depends upon the fact that the compound at the reaction of body tissue is very slowly assimilated. Therefore, when it is injected into human tissue, there is formed a depot which is slowly and gradually drawn upon by the body during the ensuing ten to twenty-four hours. The duration of the action apparently varies. In one normal nurse we found that the blood sugar was still falling at the end of ten hours after the injection. Other observations show that if a rather large amount is deposited that the blood sugar lowering action is still demonstrable for a full twenty-four hours or longer after the injection.

EFFECTS UPON THE BLOOD, URINE AND TISSUES. Local tissue changes, due to allergy, have not been observed at the Deaconess Hospital although one such case has been reported elsewhere and another in one of our discharged cases. No abscesses followed its use, and so far as we know no new areas of fatty atrophy have occurred. It has been stated that when this substance is injected into animals and the tissues are subjected to pathologic study, there is no evidence of the substance acting as a foreign body and attracting to it collections of leukocytes. There is no positive chemiotaxis. The typical effects are shown in figures 1 and 3. In figure 1 on the second day of treatment, the blood sugar fell so much during the night that a normal level was reached twenty-four hours after the dose of 50 units. On the fifth day of treatment, the morning rise in the blood sugar came under control. In figure 3 another boy's record shows control of former wide oscillations in blood sugar within a narrow range. In such severe juvenile cases there is apt to be an elevation of blood sugar during the night which sometimes develops into mild acidosis. This is prevented by this treatment.

The administration of protamine insulin is

more complicated than ordinary insulin and various precautions are necessary for its successful use. Deliberately, however, we have taught our patients to employ it and have had them carry out the mixture of the insulin with the protamine in their own homes, because if protamine insulin is to be used widely, patients must be able to make these mixtures themselves. It is true occasionally that they have made gross

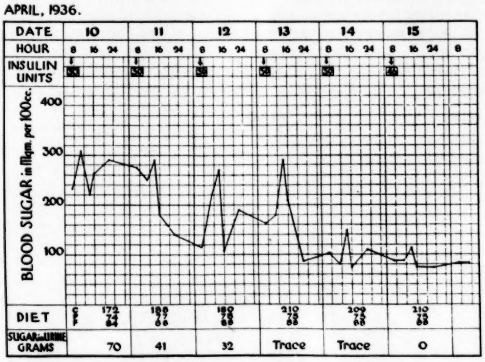

FIG. 1—Case 14484, B. W., aged eleven. Urine sugar 10 per cent. Treatment with protamine insulin only.

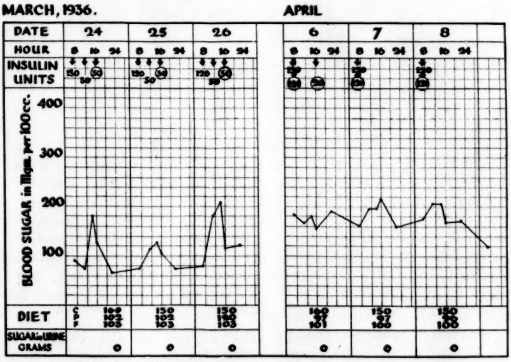

FIG. 2—Case 14483, Mrs. S., aged thirty-six, required 500 units of insulin in four doses daily for six months. The above chart shows the results of treatment with protamine insulin 120 units and ordinary insulin 120 units given simultaneously before breakfast.

and amusing errors, but it is a fact that in no instance have we felt compelled to change over our plans and arrange for the mixture of the protamine with the insulin in the hospital or office. Patients have been taught to keep the protamine insulin in the ice chest, to use only dry, cold and sterilized syringes and needles and when both old and new insulin are to be injected to make separate injections. In a few patients, we attempted to employ a needle three-quarters of an inch long and two dry syringes, injecting the old insulin first, then slightly withdrawing the needle and with a new syringe injecting the protamine insulin. This did not seem a practical method for most patients to carry out without obtaining an undesirable mixture of the two types of insulin in the tissues.

DOSAGE. The number of units of protamine insulin required for a diabetic whose disease is controlled is not materially different from the number of units of ordinary insulin no matter whether the protamine insulin is given in one or two doses. Protamine insulin acts so slowly that its full effects may not become manifest for five or six days and herein danger lies be-

cause the dose may have been increased so markedly as a result of heavy glycosuria that at the end of that period unnecessarily large amounts are being employed. Especially is one apt to obtain reactions at this time if old insulin and protamine insulin are combined before breakfast. It is so unusual for us doctors to expect our patients to have normal blood sugars early in the morning that a reaction may be precipitated if the patient receives quick-acting old insulin a half hour or more before his morning meal. Therefore, we have recently made it a rule that no patient taking old and new insulin should have it injected more than thirty minutes before taking food. It is because of the days required to adjust the diabetic to the new insulin and the possibility of reactions at the end of a few days, that we believe the general distribution of the protamine insulin should proceed slowly. However, the general control of the diabetes which it allows may counterbalance this temporary danger if doctors and patients can be taught to wait five days more or less for it to exert its complete effect.

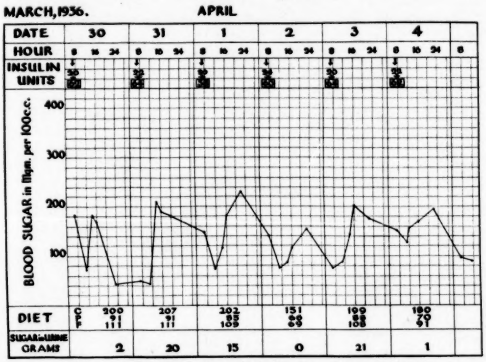

FIG. 3—Case 11905, A., aged eleven, was uncontrolled with 57 units of ordinary insulin in three doses in December, 1935. The above chart shows improved control of the blood sugar with ordinary insulin 22 units and protamine insulin 62 units taken simultaneously.

In changing from old to new insulin it is probable that in the controlled case approximately the same number of units will be employed. For the first few days following the shift the glycosuria will increase, but eventually it will disappear and in a considerable number of patients the reports have come back that the patient needs less rather than more total units than before the protamine insulin was started. By no means can this statement be made unequivocally.

The largest single dose has been 120 units, given in the fasting state simultaneously with 120 units of the ordinary insulin as shown in figure 2. The smallest dose was 5 units in a three year old girl with incipient diabetes of recent onset.

Diets. Protamine insulin works successfully even if the carbohydrate in the diet varies from 100 to 275 grams. The ideal carbohydrate would be such a value that would allow the patient to learn it readily and easily, adhere to it, and then take a quantity of protein normal for his age and size, and fat sufficient to maintain a proper weight. Undoubtedly, the individual patient can adjust the distribution of carbohydrate advantageously in various ways according to his method of living. It is our impression that an increase of 20 grams from the patient's customary amount for a single day produces fewer alterations in glycosuria than would take place when under treatment with old insulin. The diets used in eighty-eight cases included carbohydrate less than 150 grams in twenty-three cases, between 150 and 200 grams in forty-one cases, 200 to 250 grams in twenty-two cases and above 250 grams in only two cases.

Protamine Insulin Therapy. Until within a week we have believed it to be unwise to begin the use of protamine insulin on patients outside the hospital. The average period of hospital stay has been fourteen days for eighty-eight cases treated at the George F. Baker Clinic, excluding three cases with exceptionally long stays in the hospital because of complications and a group of children living in the Prendergast Preventorium. Perhaps the chief reason for insisting upon hospital observation was our desire to study effects of treatment by means of frequent blood sugar determinations and the

fact that in many patients there is a latent period of from two to five or six days during which time there is apparently little effect from the protamine insulin. During this time, one is tempted to increase the dose to a dangerously high point, as already mentioned. If this is done, then there is a sudden change on the fourth or fifth day after the beginning of treatment and a fall of blood sugar which is so rapid and may be so great that serious and persistent hypoglycemia may result. The frequency of hypoglycemia during this period of adjustment may be seen from the fact that there were 149 blood sugar determinations among a total of 1772 of 0.05 (50 milligrams) per cent or lower, four of which were 0.02 (20 milligrams) per cent. The change in character of treatment brought about by protamine insulin is well shown, because the total number of insulin injections in this group of patients was reduced from 254 to 189, or 25 per cent. This reduction does not appear so large as one might expect, because it contains a good many of the early cases in whom the reduction in number of doses was often only from four to three and also cases in whom the number of injections was not reduced at all, the end sought being the better control of the diabetes. In our more recent cases, however, a reduction of four injections a day to two injections given at the same time before breakfast has become almost the rule and therefore a much greater change in the character of treatment is wrought. In eleven patients the number of injections was reduced from four to three; in fifteen cases from four to two, and in one case, from four to one. An increased number of injections was necessary in thirteen cases entering the hospital with uncontrolled diabetes. Since April 1 the reduction in number of injections has reached a much greater per cent.

DURATION OF TREATMENT. Up to April 1, 1936, the use of protamine insulin had been discontinued in twenty-five cases, leaving sixty-six patients who had used it continuously for periods shown in table 2.

TABLE 2

DURATION OF TREATMENT WITH PROTAMINE INSULIN IN 66 CASES

Number of Months	Number of Patients
6	7
5	3
4	4
3	15
2	28
1 or less	9

Protamine insulin may be and has been omitted with safety and regular insulin substituted for it. This has taken place especially under conditions such as resulted from the floods in New England which prevented shipments. Usually a reduction in the number of units by approximately a fourth suffices to avoid the possibility of reactions. Certain patients were able to give up all insulin because of such improvement that their urine was sugar-free without insulin. Others who began protamine insulin in September and October, 1935, were discontinued because of a deliberate intention to restrict its use to hospital patients at first. A small number of patients preferred to return to their customary doses of old insulin, believing that to be equally effective in their own case.

HYPOGLYCEMIC ATTACKS. Attacks of hypoglycemia are by no means impossible when the patient is taking protamine insulin. With administration in excessive dosage, a low blood sugar level can be produced just as with regular insulin. However, the action of the new preparation is so gradual that with proper care the danger of insulin reactions is largely avoided. This has been the greatest immediate benefit that the use of protamine insulin has conferred.

When hypoglycemia arises from a single excessive dose, the effect is seen naturally eight to twenty-four hours from the time of injection. Thus a patient who is given an excessive dose in the evening before supper may wake up the next morning with a reaction. This is more apt to occur if the protamine insulin is given twice daily, as, for example, in the morning before breakfast and in the evening before supper. Then a "pyramid" effect may be seen if the doses have been too large. Early in our experience with the new insulin this occurred with one small boy, aged four and a half years, in whom we were attempting to control glycosuria solely by the use of protamine insulin in a morning and an evening dose. In an effort to control hyperglycemia in the late forenoon, the before-breakfast dose of protamine insulin was made unwisely large. Then another dose of protamine insulin was given before supper. The result was a series of hypoglycemic attacks in the early morning hours.

A word of caution should be spoken to those who adopt the system of giving regular insulin before breakfast and protamine insulin before supper. Because of the prolonged effect of the latter, the patient will awaken in the morning with a lower blood sugar level than under the old régime. Hence the action of the dose of regular insulin taken before breakfast will be more effective and unless this fact is recognized and the dosage reduced, a reaction in the late forenoon may result. Furthermore, the older insulin should be given within thirty to fifteen

minutes before breakfast to aid in the prevention of a reaction, although it must be said that even if given immediately before or after breakfast a reaction may not be averted or even ended if already begun.

With most patients hypoglycemic attacks due to protamine insulin are apt to come on more slowly thereby giving more time for intervention before marked symptoms arise. It has been supposed that patients when using the protamine insulin seem to tolerate lower levels of blood sugar for longer periods without the usual symptoms of hypoglycemia. Our own experience does not bear out this impression. Best[5] has shown that in dogs receiving protamine insulin such asymptomatic hypoglycemia may exist for eighteen to thirty hours without apparent damage to the animal and has assumed that this was so, because the tendency to lower blood sugar levels was exerted so mildly and so gradually that the bodily secretion of epinephrine was able to exert the proper counter-effect.

It is characteristic of marked hypoglycemia (in patients) due to protamine insulin that a series of reactions is apt to occur. For example, relief may be secured following the administration of carbohydrate in small amounts but some minutes later the hypoglycemic symptoms may reappear and so on. This type of action is to be expected when the blood-sugar-lowering effect is due to the gradual and continued release of insulin from a bodily depot.

Mention has been made (Editorial, Annals of Internal Medicine[6]) of the greater frequency of rather severe headache during hypoglycemia with the new insulin than with the old. We have not noticed any marked difference with our series of cases between old and new insulin. In fact, Mrs. St. C. experienced very severe headaches lasting even for three days when she had a reaction resulting from the old insulin.

Duration of Effect of Protamine Insulin. In Hagedorn's original paper and in Krarup's monograph from his clinic, it is stated that the effect of the slowly-acting insulin could be demonstrated at least twelve to fourteen hours after the injection. Subsequent experience has shown that this is a very conservative estimate. With the preparations in use at the present time an effect at least twenty-four hours distant from the time of administration is demonstrable. This is borne out by our daily experience in those patients to whom we are now giving insulin at only one time of day, viz., a dose of the regular and a dose of the protamine insulin (in different areas) before breakfast. With Wilder's case at the Mayo Clinic this prolonged action was forcefully illustrated. On the first test day the patient was given 35 units of regular insulin and her breakfast. No more insulin or food was allowed during the next twenty-four hours. On the following morning the patient was in definite acidosis, was vomiting and had a blood sugar of 425 milligrams per cent and a plasma CO_2 combining power of 28 volumes per cent. Repeated doses of regular insulin were required to bring the patient out of acidosis. Three days later the test was repeated except that an equivalent dose of protamine insulin was given before breakfast in place of regular insulin. Although the patient exhibited much glycosuria during the day, this cleared up during the night and on the following morning a single specimen of urine contained only a trace of sugar and the blood sugar was 270 milligrams per cent. The patient was clinically in good condition.

Scott and Fisher[7] have found that in animals the addition of a zinc salt to preparations of insulin further prolongs and makes more gradual the blood-sugar-lowering effect. These investigators suggest that zinc or other metals may play a part in the union between insulin and protamine, but very likely its effect may be simply to stabilize the product and make the precipitate less likely to adhere to the wall of the vial.

Beecher and Krogh[8] have made microscopic observations upon the absorption of insulin and protamine insulin.

Does Protamine Insulin Deteriorate After Four or Five Days? It is difficult to get clear-cut proof of the durability of protamine insulin solution or, on the contrary, of its deterioration, because patients who come into the hospital are under active treatment and both the diet and insulin dose are apt to be changed. In order to test this point, the protamine insulin was mixed, and a single bottle was used daily for the same patient for periods from three to ten days in length. In two cases, on the fourth and fifth days, there occurred a marked increase in sugar in the urine and a rise in the blood sugar curve. However, both were new cases so far as use of protamine insulin was concerned and might have reacted differently if the test had been carried out after a period of previous treatment with protamine insulin. The daily records of another case sometimes clearly indicated that the insulin deteriorated at the end of three, four, or five days. On the other hand, at other periods, no such evidence of deterioration appeared in his tests.

In a considerable group of patients outside the hospital who sent in daily charts no constant change in their urine tests occurred at the end of four or five days. Therefore, we do not feel certain that loss of potency actually took place. We understand that stabilizing substances are now being tried and a future gain in stability of the protamine insulin mixture is probable.

THE INDICATIONS FOR USE OF PROTAMINE INSULIN. 1. A trial should be made with diabetics of recent onset, because it is probable that such patients can be controlled with a single daily dose of protamine insulin from the beginning of treatment. Indeed it is our impression that we will never learn what protamine insulin can do until we use it as a remedy *sui generis* and observe patients treated with it exclusively over a period of years.

2. High fasting blood sugar values are a definite indication because of the great advantage to a diabetic in beginning his day with the nearly normal metabolism indicated by a normal blood sugar.

3. Multiplicity of dosage can be avoided by the use of protamine insulin, and the consequent gain in simplicity and convenience of treatment improves the end results.

4. Sensitivity to insulin as indicated by frequency of reactions constitutes the fourth major indication.

5. Hepatomegaly is an indication, because of the efficacy of protamine insulin in reducing the size of the liver, reported by Hanssen.[9]

6. Lipodystrophy may be favorably affected by the reduced number of injections and lessened acidity of the preparation.

7. Finally, it may prove to be of especial value in mild diabetics, in patients with hyperlipemia, cardiac cases in whom hypoglycemia should be avoided and for the same reason where there are occupational hazards.

CONCLUSION. With protamine insulin the fundamentals of treatment of diabetes are not changed, but the ideals of treatment are more nearly achieved. Diabetes today is a disease to be respected and neglect to do so spells disaster. Diet and exercise are as essential as ever. The patient must not overeat, but it seems likely that having determined the insulin dosage for a given quantity of carbohydrate, the protein can be determined by adjustment to the age and size of the patient, the fat regulated by body weight, and even the carbohydrate can vary ten to twenty per cent up or down with comparative impunity.

The simplicity of administration of insulin in one or two doses instead of two, three, or four doses will appeal so generally to patients that the probability is strong that the number of diabetics taking insulin will increase. As a result, the percentage of deaths from coma should fall at an accelerated pace.

The original hope that protamine insulin would be safer, because of the lessened number and severity of insulin reactions which it engenders, has been confirmed.

Thus far those diabetics characterized by high fasting blood sugar values, by the need of three or four doses of insulin or by sudden and serious insulin reactions have been those selected for trial with protamine insulin, and recently we have begun to employ it with fresh cases. Knowing that it helps severe diabetics, there is no doubt that it will help the milder cases and we are confident that soon the great majority of patients will adopt it.

Best of all is the hint that the more complete control of the disease, which the new insulin makes possible, may so raise the standard of bodily health that the diabetic will be less subject to and will resist more successfully the various so-called diabetic complications, infections, vascular degeneration and abnormal neurologic and ophthalmologic manifestations.

REFERENCES

1. Hagedorn, H. C., Jensen, B. N., Krarup, N. B., and Wodstrup, I.: Protamine insulinate. J. A. M. A. **106**:177 (Jan. 18) 1936.
2. Root, H. F., White, P., Marble, A., and Stotz, E. H.: Clinical experience with protamine insulinate. J. A. M. A. **106**:180 (Jan. 18) 1936.
3. Krarup, N. B.: Clinical Investigations into the Action of Protamine Insulin. G. E. C. Gad., Copenhagen, 1935.
4. Wilder, R. M., Kepler, E. J., Blum, B. B., and Sprague, R. G.: Clinical observations with insulin protamine compounds. To be published in J. A. M. A.
5. Kerr, R. B., Best, C. H., Campbell, W. R., and Fletcher, A. A.: Protamine insulin. Canad. M. A. J. **34**:400 (April) 1936.
6. Editorial (initialed): Ann. Int. Med. **9**:1437 (April) 1936.
7. Scott, D. A., and Fisher, A. M.: The effect of zinc salts on the action of insulin. J. Pharmacol. & Exper. Therap. **55**:206 (Oct.) 1935.
8. Beecher, H. K., and Krogh, A.: Microscopic observation of insulin and protamine insulinate. Nature **137**, 458 (March) 1936.
9. Hanssen, P.: Enlargement of the liver in diabetes mellitus. J. A. M. A. **106**:914 (March 14) 1936.

HYPOPHYSIS AND BLOOD PRESSURE

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IN 1894 Oliver and Schäfer[113] discovered that pituitary extracts raised the blood pressure; Howell[78] showed that this action was due to the posterior lobe; and in 1928 Kamm[85] and his collaborators separated the vasopressor and the oxytocic principles.* It came to be believed early that the pituitary played an important part in the regulation of the arterial pressure.[105] Azam[10] and Delille,[44] a pupil of Renon, attributed the lowered blood pressure, accelerated pulse, etc., of acute infections to an insufficiency of the pituitary, since treatment with the extract corrected these symptoms. Renon even postulated a syndrome of hyperpituitarism with hypertension and bradycardia. But in spite of many theories there were few facts to support them, and in 1932 Dale[41] concluded that it was not possible to say what part the vasopressor principle in the posterior lobe played in the maintenance of normal blood pressure. Nevertheless numerous experimental and clinical observations indicate that there may be a relation between the pituitary and the blood pressure level. We will describe and discuss these observations in this paper.

ARTERIAL BLOOD PRESSURE IN EXPERIMENTAL PITUITARY INSUFFICIENCY

Amphibians.—The toad's pituitary contains substances which raise the blood pressure of the dog,[72, 76] the cat[64] and the toad.[114] The neuro-intermediate lobe is more active than the principal lobe in this respect.[114] The vascular system of the batrachians is sensitive to the vasopressor substance in the mammalian pituitary,[1, 14, 55, 74, 93, 113, 114, 118, etc.] but Hogben and Schlapp[69] had to use such large quantities to produce effects, that it was not possible to consider them physiological.

A few hours after complete extirpation of the pituitary in the toad the capillaries and arterioles of the skin become dilated.[9, 94] Injection or perfusion of pituitrin, even in doses of 1 : 1,000,000 re-establishes the capillary tone and larger doses produce a contraction of the arterioles as well. From these facts Krogh[93] deduced that the pituitary, by means of a hormone, had a continuous action on the tone of the capillaries.‡

The removal of the principal lobe produces a similar but transitory alteration,[9, 94] since the normal tone is soon recovered,[94] though in some cases the recuperation may not be complete.[9] In the toad when the nutritional disturbances and asthenia are marked, usually about one month after the lobectomy, the vasodilatation again becomes pronounced. Infundibulotuberal lesions produce only a moderate and passing dilatation.[9] The dilated capillaries are unstable,[94] but react well to thermal stimuli.[9] According to Nogaki,[111] however, the contractile capacity of the vascular system is reduced in the hypophysectomized frog.

Blount[23] produced a state of hyperpituitarism in the larvae of *Amblystoma,* by grafting two extrahypophyseal anlagen. In these animals he observed vasoconstriction, bradycardia, hypertrophy of the ventricle, and sometimes edema. The basal membrane of the glomeruli of the kidney was thickened, the glomeruli were diminished in size and in some the capillaries became obstructed; these lesions are similar to those seen in human hypertension.[23]

Orias has done important work in our Institute, showing that the intermedio-neural lobe plays a considerable rôle in the maintenance of normal blood pressure in the toad *Bufo arenarum* (Hensell). Removal of the principal lobe alone did not alter the blood pressure until the nutritional disturbances and neuromuscular asthenia appeared, when it was found somewhat lower (30 mm. Hg.) than in the controls which had only been craniotomized (39 mm. Hg.). (Fig. 1.) When the whole pituitary was removed, i.e., the neuro-intermediate together with the principal lobe, the blood pressure began to fall within a few hours after the operation. At times there was a transitory reaction in about twenty-four hours, but afterwards the decrease continued and an average blood pressure of 24 mm. Hg. was found one week after operation and of 17 mm. one month later. The injection of extracts of either lobe raised the blood pressure but the neuro-intermediate was the more active. The fall in blood pressure could be prevented by daily implantation of one lobe, either glandular or neuro-intermediate. Neubach (unpublished data) showed that intravenous injection of 3 cc. arterial blood from a normal toad produced a significantly greater increase in the blood pressure of hypophysectomized toads than did the same quantity of blood from hypophysectomized toads.

Several facts indicate that the vasopressor and melanophore dilating activities are due to different substances. The following evidence

*Extensive bibliographies on the vasopressor activity of pituitary extracts will be found in Houssay,[74] Geiling,[57] Trendelenburg.[146] My own work on the subject will be found in my book.[74]

†Houssay, Bernardo A.—Professor of Physiology, Faculty of Medical Sciences, University of Buenos Aires, 1919–. For record and address of author see "This Week's Issue," page 946, issue of May 7.

‡Krogh also brings evidence for the presence of the hormone in the blood of mammals. Thus, in ox serum there is a substance which constricts the capillaries; it is dialyzable, insoluble in alcohol and ether, soluble in methyl alcohol and thermostable.

may be so interpreted, namely, that after removal of the pituitary the skin blanches before the blood pressure drops; that there are certain differences in the pharmacological and chemical characteristics of the two hormones;[45, 46, 47, 54, 56, etc.] and, of even more significance, that Dietel[45, 46] has isolated a melanophore dilating substance which, far from having a pressor effect, dilates

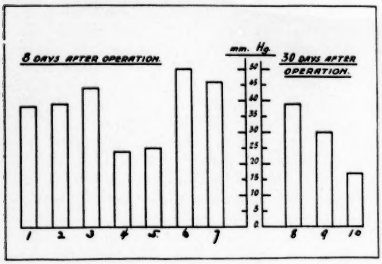

FIG. 1.
Blood pressure of toads in mm. Hg.
Eight days after operation.
1. Controls.
2. Removal of principal lobe.
3. Lesion of tuber cinereum.
4. Hypophysectomy.
5. Hypophysectomy and lesion of tuber cinereum.
6. Hypophysectomy and implantation of neuro-intermediate lobe.
7. Hypophysectomy and implantation of principal lobe.
Thirty days after operation.
8. Controls.
9. Removal of principal lobe.
10. Hypophysectomy.

the capillaries and decreases the blood pressure. He believes it may also have a part in regulating the blood pressure.

Mammals. — Braun Menendez[24, 25, 26] measured the blood pressure in twenty-five hypophysectomized dogs in our Institute. Only three of the operated animals had a normal blood pressure and the average value (108 mm. Hg.), was lower than that found in twenty-one normal controls (127 mm. Hg.). Lesions of the tuber did not modify the blood pressure, the average being 124 mm. Hg. in thirteen experiments, nor did the removal of the posterior lobe produce a significant decrease, the average being 120 mm. Hg. in four dogs. (Fig. 2.) It must be noted that in these experiments the extirpations were not complete, since the *pars tuberalis* remained in the hypophysectomized animals, and in those whose posterior lobe alone was removed, fragments of the *pars intermedia* were left behind.*

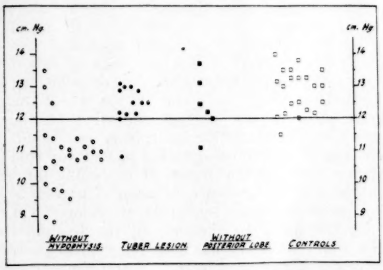

FIG. 2.
Blood pressure of dogs in cm. Hg.

Braun Menendez[25, 26] was able to demonstrate that the vasomotor reactions were less adequate in the hypophysectomized than in normal dogs. When dogs were bled from the carotid to the extent of 1.5 per cent of the body weight the blood pressure fell 30 to 40 mm. Hg. In six experiments on normal animals the pressure returned to its initial level in 25 to 75 (average 45) minutes, whereas in nine experiments on hypophysectomized animals the initial pressure was not re-established until 75 to 130 (average 95) minutes following bleeding. (Fig. 3.)

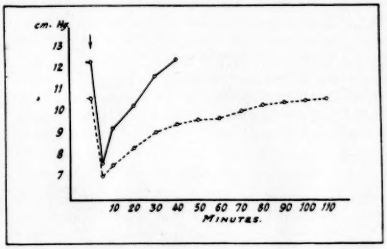

FIG. 3.
Graph showing the effect of hemorrhage on the blood pressure of normal and hypophysectomized dogs.
Solid line—average of five normal dogs.
Dotted line—average of nine hypophysectomized dogs.
At arrow the animals were bled from the carotid artery to the extent of 1.5 per cent of the body weight.
Abscissae—Time in minutes.
Ordinates—cm. Hg.

In the rat, removal of the posterior lobe does not alter the blood pressure significantly, the observed pressures being within the normal range, though somewhat low. Their sensitivity to histamine also is not increased. On the other hand complete hypophysectomy is followed by a decrease in blood pressure and there may be a lowered resistance to histamine.[53] Yamashita[154] also found a lowered blood pressure in the rabbit after partial hypophysectomy.

BLOOD PRESSURE IN HUMAN PITUITARY INSUFFICIENCY

In patients with chromophobe adenomas of the pituitary the systolic pressure is usually low.[11, 36, 71, 116] Cushing[36] found it to be below

*Before Braun Menendez did his work I had measured the blood pressure in a hypophysectomized dog in 1921 and Koster and Geesink[90] did the same in two dogs. Braun Menendez used Biasotti's method, which measures the systolic pressure.[20]

100 mm. Hg. in 11 per cent and below 110 in 46 per cent of his 200 cases, while only two had an abnormally high blood pressure. In craniopharyngiomas it is lower still. Perémy[120] found the blood pressure to be between 78 and 110 mm. Hg. in 20 out of 45 cases of hypophyseal tumor.

In many cases of pituitary cachexia there is a low blood pressure, as noted in the papers by Graubner,[59] Calder[30] and others more recently. The vasomotor reactions are also disturbed.[132] After muscular exercise both the systolic and diastolic pressures fall markedly, and the same may happen when the patients resume the erect posture after a period of reclining. This circulatory collapse frequently occurs in such patients and may be corrected by treatment with anterior lobe extract. Nevertheless it cannot be attributed specifically and primarily to the hypophysis, since it is a common occurrence in other types of cases which have a low blood pressure and marked loss of weight. Thus, it has been seen in hypothyroidism and in cases of tabes dorsalis. In spite of this, Schelling believes that the pituitary anterior lobe is of importance in the regulation of blood pressure. Ratner[125] found these circulatory disturbances in ten cases, and attributes them to adrenal insufficiency due to a deficient secretion of the pituitary adrenotropic hormone.

BLOOD PRESSURE IN ACROMEGALY

The postmortem examination of acromegalics often reveals arteriosclerosis and enlargement of the heart. Numerous instances of increased blood pressure have been reported in these patients[2, 8, 31, 32, 40, 63, 80, 108, 115, 117, 119, 121, 122, 155] and death is frequently due to cardiac insufficiency. Nevertheless the pressure was low (below 120 mm. Hg.) in 30 out of 100 cases of acromegaly studied by Davidoff[43] and in 28 per cent of those seen by Rowe and Lawrence.[129] According to Kylin,[97] in cases of acromegaly occurring in Sweden and collected by Brennig, the blood pressure was normal in young subjects, in only two was it above 140 mm. Hg., but in the patients forty or more years old 11 per cent of the men and 60 per cent of the women had a high blood pressure. Henstell[63] says that paroxysmal hypertension may occur in acromegalics.

PITUITARY BASOPHILISM AND THE BLOOD PRESSURE

We owe to Cushing the recognition of a clinical syndrome characterized by adiposity, dorsocervical kyphosis, amenorrhea or impotence, hypertrichosis, plethoric skin with atrophic striae, high blood pressure, glycosuria, osteoporosis, etc. At autopsy a basophile adenoma of the pituitary is found in a large proportion of the cases in the literature which I have read. The raised blood pressure was evident and constant in the reports of seventeen cases confirmed by autopsy and in which the blood pressure was recorded.[3, 12, 22, 33, 35, 38, 88, 98, 110, 126, 127, 130, 131, 141, 150, 151] Some of the literature I have not been able to read[16, 58, 142, etc.] and in numerous published cases there was no anatomical verification.

Certain improvements which occur when the pituitary is irradiated favor the theory that it is the prime factor of this disease (Cushing, Jamin, Dattner, Wohl and collaborators, Aub, etc.). Even though the basophile adenoma is not constant (according to Bauer[13] it was found in only fifteen out of twenty-three cases) its frequency is significant since in general it is a rare condition, Susman[140] finding it in only 3 per cent of the 260 pituitary glands which he examined. In some cases adenoma was not present but there was an increase in the basophile cells; this is an equivalent pathological state according to Cushing. In discussing the possible part the pituitary might take in the genesis of raised blood pressure he considers that the hypertension might be due (1) to a specific secretion of the adenoma, (2) to stimulation of the pressor secretion of the posterior lobe by the adenoma, (3) to an action through some other gland. Cushing[38, 39] is inclined to accept the second of the possibilities just mentioned, while Bauer[13] maintains that elevation of pressure is due to adrenal hyperactivity brought about by the pituitary adrenotropic hormone.

Cushing[39] observed that in cases of eclampsia and elevated blood pressure and in certain cases of basophilism with hypertension, there was basophile cell infiltration of the posterior lobe. This might indicate hyperactivity of this lobe, but, according to Spark,[137] this morphological appearance has no significance. He made an extensive study of reported cases and sectioned the pituitary in seventy cases of raised blood pressure, in eleven with a previous history of raised blood pressure and in 108 where the blood pressure was normal; in all types of cases a similar basophilic infiltration was found. Also Butt,[28] in 200 cases, failed to find any correlation between the degree of basophilic infiltration and the presence of arterial hypertension, arteriosclerosis, eclampsia or obesity. On the other hand an increase in the basophile cells of the pituitary has been reported in cases of raised blood pressure[19, 91, 92] and more frequently in adiposity. Kraus[91] found it in 80 per cent of cases of the latter type and believed that the basophilism was secondary to the obesity. In some cases of adrenal tumor the fact that foci of basophile cells without adenoma[18, 100*] have been found in the pituitary

*In these cases it may be supposed that pituitary basophilism was the cause of the adrenal adenomas, which later became malignant.

has suggested the possibility that basophilism may be secondary to overactivity of the adrenal. Finally, Leyton[104] found Cushing's syndrome in a case of thymus tumor associated with adrenal hyperplasia.

It is known that the presence of the anterior pituitary is necessary for the development and maintenance of the normal anatomical and functional state of the adrenal cortex.[75] Hypophysectomy causes the atrophy of the reticular layers and of the internal part of the fascicular layers, with preservation or hypertrophy of the glomerular zone, but leaves the medulla unchanged. Adrenotropic extracts of the pituitary may bring about the hypertrophy of the adrenal cortex[15, 34, 50, 51, 75, etc.] and even produce small adenomas[123] and certain symptoms (adiposity, bony alterations, etc.), which Thompson and Cushing[144] consider similar to those of basophilism. Up to now it has not been observed that they cause a rise in blood pressure.

Bauer[13] attributes the symptoms of Cushing's syndrome to hyperactivity of the adrenal cortex, due to an overproduction of the adrenotropic pituitary hormone. He refuses to accept the theory that it originates in the basophile cells, citing the frequency of basophilism in different circumstances and the fact that Sokolow and Gromow[136] found a cortico-adrenal syndrome with raised blood pressure in a child, which was found to have an eosinophile adenoma of the pituitary. The anatomical state of a gland does not give an adequate measure of its function; for this reason a possible overactivity of the pituitary or the adrenal glands cannot be excluded in those cases where no basophile adenoma or adrenal hypertrophy is found. It would be necessary to measure the amount of hormones secreted into the blood. Bauer[13] further draws attention to the fact that the symptoms of Cushing's syndrome are also those of hyperactivity of the adrenals. In chromaffin tumors of adrenal origin the blood pressure is raised permanently or paroxysmally, and in six cases in which the tumor was removed the paroxysms disappeared. It has not been proved that permanent hypertension is due to an excessive secretion of adrenin. Probably cortical overactivity also causes the blood pressure to rise, since there are cases of tumors of the adrenal cortex with high blood pressure and hyperglycemia and in some instances removal of the tumor has cured these symptoms. It must also be remembered that in certain cases of Cushing's syndrome the adrenals are normal, although generally they are hypertrophied or adenomatous.

The adrenal symptoms are predominant in the syndrome of basophilism, but it cannot be affirmed that the hyperactivity of the adrenals is always of pituitary origin, although the large number of typical and marked cases with basophile adenoma of the pituitary is suggestive. It can only be suspected that the latter is the primary cause in many cases. It is not yet clear whether the raised blood pressure is due to an excess of adrenal or pituitary hormones or to some other cause, since the presence of these hormones in the blood has not yet been confirmed.

THE PITUITARY AND RAISED BLOOD PRESSURE IN THE TOXEMIAS OF PREGNANCY AND IN ECLAMPSIA

Since Hofbauer's work[66] it has been maintained that eclampsia may be due to a polyglandular disturbance, with an excess of the posterior pituitary lobe secretion predominating. The principal arguments brought forward and some of the objections raised to them are as follows: (1) There is a certain similarity between the symptoms of eclampsia and those which are produced by posterior lobe extract,[5, 49, 52, 66, 95, 102, 128, 147, etc.] (e.g. tendency to edema, raised blood pressure, capillary spasm, convulsions and coma, pulmonary edema, ionic changes, favorable action of narcotics), but there are also definite differences.[21, 143] (2) There is a certain similarity between the anatomical lesions found in eclampsia (in the liver, kidney, etc.) and those provoked by posterior pituitary extract.[52, 89] However the majority of writers consider these lesions rare and hardly worth mentioning.* (3) The infiltration of the posterior lobe by basophile cells in eclamptics would cause oversecretion of pituitrin,[39] but Spark[137] proved that the basophile invasion may occur when eclampsia is not present. (4) Dialysis of the serum of eclamptics shows that there is an increase in antidiuretic and blood pressure raising substances[5] but this cannot be pituitary posterior lobe secretion (Theobald[143]). The blood of eclamptics, when injected into the cerebral ventricles, causes oliguria according to Marx.[106] The antidiuretic action, however, has not been confirmed in the careful experiments of Byrom and Wilson[29] or of Hurwitz and Bullock.[81] (5) The melanophore dilating substance is increased in the blood[95] and placenta[49] of eclamptics. Against this are the reports that the blood of eclamptics, in common with that of normal or pregnant women, possesses the property of neutralizing the effects of certain of the posterior pituitary lobe extracts, for example the oxytocic,[53, 145, etc.] the oliguric,[21] the melanophore dilatory[45] and the pressor.[134]

THE PITUITARY AND OTHER HYPERTENSIONS

An increase of basophile cells has been seen in the hypophyses of two-thirds of the cases of raised blood pressure,[19] but is even more fre-

*For the older literature see Houssay[74] and for the more recent Ohligomacher[112] and Scheps.[132]

quent in obesity,[91] and has also been observed in other conditions. Spark[137] declares that the posterior pituitary lobe invasion by basophile cells described by Cushing[38, 39] can exist with equal frequency when there is no raised blood pressure.

Kylin[97] believes that the anterior pituitary lobe is an essential factor in hypertension, because the general and metabolic symptoms are exactly opposite to those of pituitary insufficiency. Pal,[116] and Merle and his collaborators[107] also believe in the pituitary theory and Drouet[48] describes improvement in certain cases of raised blood pressure due to irradiation of the pituitary. The cerebrospinal fluid of patients suffering from raised blood pressure only occasionally contains "minute traces of pituitrin",[79] so an overactivity of the posterior pituitary lobe does not seem to be an etiological factor in the disease. Moehlig[109] has produced arteriosclerosis in rabbits, by submitting them to a diet rich in fats and cholesterol combined with treatment with pituitrin. Volhard[148] has shown that the raised blood pressure due to ligature of the renal artery is produced both in normal and hypophysectomized dogs.

PITUITARY, DIENCEPHALON AND HYPERTENSION

It has been known for some time* that the principal vasomotor centres are in the medulla. Section of the brain stem above the pons does not modify the level of the blood pressure or the vasomotor reflexes and reactions[25, 26, 65, 86, 138, 139, etc.] in acute experiments.

The stimulation of the posterior ventral part of the hypothalamus causes a marked rise of blood pressure,[17, 77, 82, 84, 86, 124, 149] even in the absence of the pituitary and adrenals. (Karplus and Kreidl, confirmed in our Institute.) When the adrenals are present there is also a marked secretion of adrenin, itself capable of raising the blood pressure[77] and the blood sugar.[82] The melanophore dilating substance in the cerebrospinal fluid is also increased.[87] Ergotamine or the extirpation of the sympathetic chain and the splanchnics[82] suppresses the rise in blood pressure. Leiter and Grinker[101] affirm that the rise in blood pressure occurs only when there are muscular or respiratory disturbances, but de Jaegher and Van Bogaert[82] have shown that it may be raised both by mechanical and chemical stimuli whieh do not evoke muscular activity. According to Hoff and Urban[67] lesions of the mammillary bodies may cause a delayed rise in blood pressure some months after the operation.

It has not been proved that the pituitary takes part in the rise in blood pressure produced by cisternal injection of kaolin or other colloids.[60, 61, 70] Pituitrin causes a rise of blood pressure if it is injected into the cerebrospinal canal[74, 99] or the cistern.[61, 62] If, however, it is injected into the ventricles there is either a fall in blood pressure followed by a rise[37] or no effect at all.[63]

*For bibliography see Braun Menendez.[26]

GENERAL SUMMARY

The posterior pituitary lobe contains vasopressor substances, which in amphibians play a very important rôle in the maintenance of the blood pressure and arterial and capillary tone. Small quantities of similar substances exist in the principal lobe of the toad, but removal of this lobe causes a lowering of the blood pressure only after asthenia has developed. In the rat, dog and man pituitary insufficiency is accompanied by lowered blood pressure; it is not clear whether this is due to lack of one or both lobes, but it seems more particularly due to lack of the anterior lobe (central or peripheral vascular asthenia).

The existence of raised blood pressure in acromegaly has not been well established, since the blood pressure is frequently normal in these cases. On the other hand hypertension is a constant and prominent symptom in the pituitary basophilism syndrome of Cushing, though whether this is due to pituitary or adrenal hypersecretion or to a secondary or associated factor, is not yet clear.

The evidence put forward to demonstrate that hyperactivity of the posterior pituitary lobe is the causal factor in eclampsia and in essential hypertension is contradictory and inconclusive.

In contradistinction to the medulla the diencephalon is not essential for the maintenance of blood pressure in acute experiments, nor has it been proved that increase in blood pressure due to lesions or stimulation of this region is accompanied by hypersecretion of the posterior pituitary.

REFERENCES

1. Adler, L.: Arch. f. exper. Path. u. Pharmakol. **91**:81, 1921.
2. Alessandri: Policlinico, prat. **31**:913, 1908.
3. Anderson, J.: Glasgow M. J. **83**:178, 1915.
4. Anselmino, K. J.; Herold, L., and Hoffmann, F.: Ztschr. f. d. ges. exper. Med. **94**:323, 1934; Klin. Wchnschr. **13**:1724 (Dec. 1) 1934; Arch. f. Gynäk. **158**:531, 1934.
5. Anselmino, K. J., and Hoffmann, F.: Arch. f. Gynäk. **144**:503, 506, 1931; **147**:597, 621, 652; Zentralbl. f. Gynäk. **58**:2363 (Oct. 6) 1934; Klin. Wchnschr. **10**:1438 (Aug. 1) 1931.
6. Anselmino, K. J.; Hoffmann, F., and Herold, L.: Klin. Wchnschr. **12**:1944 (Dec. 16) 1933; **13**:209 (Feb.) 1934; Arch. f. Gynäk. **157**:86, 1934.
7. Anselmino, K. J.; Hoffmann, F., and Kennedy, W. P.: Edinburgh M. J. **39**:376 (June) 1932.
8. Atkinson, F. R. B.: Acromegaly. London: Bale. 1932.
9. Aubrun, E. A., and Porto, J.: V Congreso Nac. Medicina. Rosario **3**:254, 1934.
10. Azam, J.: Thèse Fac. Med. Paris. 1907.
11. Barker, L. F.: Endocrinol. **17**:647 (Nov.-Dec.) 1933.
12. Bauer, J.: Wien. Klin. Wchnschr. **43**:582 (May 8) 1930.
13. Bauer, J.: Klin. Wchnschr. **14**:361 (March 16) 1935.
14. Bauer, J., and Fröhlich, A.: Arch. f. exper. Path. u. Pharmakol. **84**:33, 1918.
15. Baumann, E. J., and Marine, D.: Proc. Soc. Exper. Biol. & Med. **29**:1220 (June) 1932.
16. Baumgartner, L.: Yale J. Biol. & Med. **7**:327 (March) 1935.
17. Beattie, J.; Brow, G. R., and Long, C. N. H.: Proc. Roy. Soc. London **106**:253 (May 3) 1930.
18. Bengolea, A. J., and Martinez de Hoz, R.: Rev. Med. Quir. Patol. Femen. (Bs. As.) **2**:340, 1934.

19. Berblinger, W.: Hirsch. Handb. inn. Sekretion. **1**:909, 1932; Virchows Arch. f. path. Anat. **275**:230, 1930.
20. Biasotti, A.: Compt. rend. Soc. de biol. **97**:598 (July 22) 1927; Tesis Fac. Med. Bs. As. 1927.
21. Bickenbach, W., and Rupp, H.: Arch. f. Gynäk. **155**:572, 1934.
22. Bishop, P. M. F., and Close, H. G.: Guy's Hosp. Rep. **83**:143 (April) 1933.
23. Blount, R. F.: Anat. Record 55 (Supp.) 7, 1932-33; J. Exper. Zoöl. **63**:113, 1932; Proc. Soc. Exper. Biol. & Med. **32**:650 (Jan.) 1935.
24. Braun Menendez, E.: Rev. Soc. argent. de biol. **8**:463, 1932; Compt. rend. Soc. de biol. **111**:477, 1932.
25. Braun Menendez, E.: Rev. Soc. argent. de biol. **10**:204, 1934; Compt. rend. Soc. de biol. **117**:453, 1934.
26. Braun Menendez, E.: Tesis Fac. Med. Bs. As. 1934; Rev. argent. de cardiol. **1**:337, 1934.
27. Bugbee, E. P., and Kamm, O.: Endocrinol. **12**:671, 1928.
28. Butt, E. M.: Am. J. Pathol. **11**:891, 1935.
29. Byrom, F. B., and Wilson, C.: Quart. J. Med. **3**:361 (July) 1934.
30. Calder, R. M.: Bull. Johns Hopkins Hosp. **50**:87 (Feb.) 1932.
31. Claude, H.: Compt. rend. Soc. de biol. **59**:362, 1905.
32. Claude, H., and Baudouin, A.: Compt. rend. Soc. de biol. **71**:75, 1911.
33. Close, H. G.: Brit. M. J. **1**:256 (Feb.) 1935.
34. Collip, J. B.; Anderson, E. M., and Thompson, D. L.: Lancet **2**:347 (Aug. 12) 1933.
35. Craig, J., and Cran, B. S.: Quart. J. Med. **3**:57 (Jan.) 1934.
36. Cushing, H.: Lancet **2**:119, 175 (July 19) 1930.
37. Cushing, H.: Proc. Nat. Acad. Sc. **17**:163 (April 15) 1931.
38. Cushing, H.: Bull. Johns Hopkins Hosp. **50**:137, 1932; J. A. M. A. **99**:281, 1932; Arch. Int. Med. **51**:487, 1933; Pituitary Body, Hypothalamus and Parasympathetic Nervous System. Thomas. 1932.
39. Cushing, H.: Proc. Soc. Exper. Biol. & Med. **30**:1424 (June) 1933; Am. J. Path. **9**:539, 1934; **10**:145, 1934.
40. Cushing, H., and Davidoff, L. M.: Monograph 22, Rockefeller Inst. Med. Research. New York. 1927.
41. Dale, H. H.: Arch. f. exper. Path. u. Pharmakol. **167**:21, 1932.
42. Dattner: Quoted by Bauer, 1935.
43. Davidoff, L. M.: Endocrinol. **10**:467, 1926.
44. Delille, A.: Thèse Fac. Med. Paris. 1909.
45. Dietel, F. G.: Klin. Wchnschr. **12**:1683 (Oct. 28) 1933; Arch. f. Gynäk. **157**:534, 1934.
46. Dietel, F. G.: Arch. f. exper. Path. u. Pharmakol. **170**:417, 1933; Klin. Wchnschr. **13**:554 (April 14) 1934.
47. Dreyer, N. B., and Clark, A. J.: J. Physiol. **58**: Proc. XVIII. 1923.
48. Drouet, P. L.: Bull. et mém. Soc. med. d. hôp. de Paris **50**:139 (Feb. 12) 1934.
49. Ehrardt: Quoted by Fauvet.[52]
50. Emery, F. E., and Atwell, W. J.: Proc. Soc. Exper. Biol. & Med. **31**:200 (Nov.) 1933; Anat Rec. **58**:17 (Dec. 25) 1933.
51. Emery, F. E., and Winter, C. A.: Anat. Rec. **60**:381 (Nov. 25) 1934.
52. Fauvet, E.: Arch. f. Gynäk. **144**:502, 1931; Klin. Wchnschr. **10**:2125, 1931; **185**:100, 1933.
53. Fekete, K.: Endokrinol. **10**:16-23 (Jan.) 1932.
54. Fenn, W. O.: J. Physiol. **59**:395, 1924.
55. Fodera, F. A., and Pittau, L.: Arch. ital. de. Biol. **52**:370, 1909.
56. Gaddum, J. H.: J. Physiol. **65**:434 (Aug.) 1928.
57. Gelling, E. M. K.: Physiol. Rev. **6**:62 (Jan.) 1926.
58. Gouley, B. A.: Ann. Int. Med. **8**:1294 (April) 1935.
59. Graubner, W.: Ztschr. Klin. Med. **101**:249, 1925.
60. Hamperl, H., and Heller, H.: Arch. f. exper. Path. u. Pharmakol. **173**:283, 1933; **174**:517, 1934.
61. Heller, H.: Arch. f. exper. Path. u. Pharmakol. **173**:291, 1933; Klin. Wchnschr. **12**:1260, 1933; **13**:241, 1934.
62. Heller, H., and Kusunoki, G.: Arch. f. exper. Path. u. Pharmakol. **173**:301, 1933.
63. Henstell, H.: Yale J. Biol. & Med. **5**:531 (July) 1933.
64. Herring, P. T.: Quart. J. Exper. Physiol. **6**:73, 1913.
65. Hermann, H., and Jourdan, F.: Compt. rend. Soc. de biol. **107**:706 (June) 1931; **114**:1254, 1933.
66. Hofbauer, J.: Zentr. Gynak. **43**:745 (Oct.) 1918.
67. Hoff, H., and Urban, H.: Klin. Wchnschr. **12**:1366 (Sept. 2) 1933.
68. Hoffmann, F., and Anselmino, K. J.: Arch. f. Gynäk. **147**: 604, 1931; Klin. Wchnschr. **10**:1442 (Aug. 1) 1931.
69. Hogben, L. T., and Schlapp, W.: Quart. J. Exper. Physiol. **14**:229, 1924.
70. Högler, F.: Uberrack, K.; Zell, F., and Falta, W.: Klin. Wchnschr. **13**:255 (Feb. 17) 1934.
71. Holmes, G.: Brit. M. J. **2**:1035 (Dec. 4) 1926.
72. Houssay, B. A.: Rev. Univ. Bs. As. **13**:89, 1910; Argent. Médica **8**:229, 1910; Trab. Labor. Fisiol. Fac. Med. Bs. As. **1**:95, 1910.
73. Houssay, B. A.: Tesis Fac. Med. Bs. As. 1911.
74. Houssay, B. A.: La accion fisiologica de los extractos hipofisarios. 1918; 2a edic. 1922; Bs. As. Flaiban edit.
75. Houssay, B. A.: Prensa Médica Argent. **20**:1563, 1933.
76. Houssay, B. A.; Giusti, L., and Lahille, R.: Rev. Circ. Med. Argent. y Centro Estud. Med. **12**:257, 1912.
77. Houssay, B. A., and Molinelli, E. A.: Rev. de la Soc. argent. de biol. **6**:600, 1925; Compt. rend. Soc. de biol. **93**:1454 (Oct. 8) 1925.
78. Howell, W. H.: J. Exper. Med. **3**:245, 1898.
79. Hoyle, C.: Quart. J. Med. **2**:549 (Oct.) 1933.
80. Humphry, L., and Dixon, W. E.: Brit. M. J. **2**:1047 (Oct. 8) 1910.
81. Hurwitz, D., and Bullock, L. T.: Am. J. M. Sc. **189**:613, 1935.
82. de Jaegher, M., and Van Bogaert, A.: Compt. rend. Soc. de biol. **118**:544, 546, 1033, 1035, 1935.
83. Jamin, F.: München med. Wchnschr. **81**:1045 (July) 1934.
84. Kabat, H.; Magoun, H. W., and Ranson, S. W.: Proc. Soc. Exper. Biol. & Med. **31**:541 (Feb.) 1934.
85. Kamm, O.; Aldrich, T. B.; Grote, I. W.; Rowe, L. W., and Bugbee, E. P.; J. Am. Chem. Soc. **50**:573, 1928.
86. Karplus, J. P., and Kreidl, A.: Pflügers Arch. **171**:192, 1918; **203**:533, 1924; **215**:447, 615, 1927; Skand. Arch. Physiol. **49**:157, 1926.
87. Karplus, J. P., and Peczenick, O.: Pflügers Arch. **225**:654, 1930.
88. Kepler, E. J.; Kennedy, R. L.; Davis, A. C.; Walters, W., and Wilder, R. M.: Proc. Staff Meet. Mayo Clin. **9**:169 (March) 1934.
89. Knepper, R.: Klin. Wchnschr. **13**:1751 (Dec. 8) 1934.
90. Koster, S., and Geesink, A.: Arch. f. d. ges. Physiol. **217**:293, 1928.
91. Kraus, E. J.: Med. Klin. **29**:449, 1933; Klin. Wchnschr. **13**:487 (March) 1934.
92. Kraus, E. J., and Traube, O.: Virchows Arch. f. path. Anat. **289**:315, 1929.
93. Krogh, A.: The Anatomy and Physiology of Capillaries. New Haven: Yale University Press. 1922.
94. Krogh, A., and Rehberg, P. B.: Compt. rend. Soc. de biol. **87**:461, 1922.
95. Küstner, H.: Arch. f. Gynäk. **133**:331, 1928; **144**:514, 1931.
96. Küstner, H., and Biehle, H.: Arch. f. Gynäk. **131**:274, 1927.
97. Kylin, E.: Med. Klin. **29**:1004, 1933; **30**:153, 1934; Deutsches Arch. f. klin. Med. **176**:301, 1934; Klin. Wchnschr. **14**: 470, 1935; Ztschr. f. Kreislauforsch. **27**:1 (Jan.) 1935.
98. Lawrence, J. H., and Zimmerman, H. M.: Arch. Int. Med. **55**:745, 1935.
99. Leimdorfer, A.: Arch. f. exper. Path. u. Pharmakol. **118**:253. 1926.
100. Lescher, F. G.: Proc. Roy. Soc. Med. **27**:281, 1934.
101. Leiter, L., and Grinker, R. R.: Arch. Neurol. & Psychiat. **31**:54, 1934.
102. Lévy-Solal, E.; Coen, A., and Lauret, G.: Compt. rend. Soc. de biol. **119**:294, 1935.
103. Lévy-Solal, E., and Laudat, M.: Presse méd. **43**:603 (April) 1935.
104. Leyton, O.: Lancet **1**:1221 (June) 1934.
105. Livon, C.: Compt. rend. Soc. de biol. **50**:98 (Jan.) 1898.
106. Marx, H.: Klin. Wchnschr. **14**:367 (March 16) 1935.
107. Merle, E.; Petit, G., and Prelle, M.: Rev. franç. d'endocrinol. **13**:173 (June) 1935.
108. Messedaglia, L.: Studi sull 'acromegalia. Padova. 1908.
109. Moehlig, R. C., and Osius, E. A.: Ann. Int. Med. **4**:578, 1930; Endocrinol. **14**:337, 1930.
110. Moehlig, R. C.: J. A. M. A. **99**:1498 (Oct. 29) 1932.
111. Nogaki, S.: Arch. f. exper. Path. u. Pharmakol. **103**:147, 1924.
112. Ohligomacher, H.: Klin. Wchnschr. **12**:1404 (Sept.) 1933.
113. Oliver, G., and Schäfer, E. A.: J. Physiol. **16**:(Proc.) 1, 1894; **18**:277, 1895.
114. Orias, O.: Rev. Soc. argent. de biol. **10**:91, 1934; Compt. rend. Soc. de biol. **116**:894, 1934.
115. Packard, M.: Am. Med. **5**:539, 1910. Cit. Henstell.
116. Pal, J.: Med. Klin. **30**:698, 1934.
117. Parisot, J.: Arch. d. mal. du coeur 421, 1908.
118. Parisot, J., and Mathieu, P.: Compt. rend. Soc. de biol. **76**:222, 1914.
119. Payenneville, and Cailliau, P.: Presse méd. **39**:380 (March 14) 1931.
120. Perémy, G.: Klin. Wchnschr. **14**:92 (Jan. 19) 1935.
121. Perlia, G., in Kraus, Brugsch Spez. Pathol. u. Ther., inn. Krankh. **1**:627, 1919.
122. Phillips, J.: M. Rec. **75**:301 (Feb. 20) 1909. Cit. Henstell.
123. Putnam, T. J.; Benedict, E. B., and Teel, H. M.: Arch. Surg. **18**:1708, 1929.
124. Ranson, S. W.; Kabat, H., and Magoun, H. W.: Arch. Neurol. & Psychiat. **33**:467 (March) 1935.
125. Ratner, J.: Ztschr. f. klin. Med. **127**:713, 1935.
126. Reichmann, V.: Deutsche Arch. Klin. Med. **130**:133, 1919.
127. Roch, M.: Presse méd. **42**:987 (June) 1934.
128. Rossenbeck, H.: Schweiz. med. Wchnschr. **57**:1067, 1927; Klin. Wchnschr. **9**:1545, 1930.
129. Rowe, A. W., and Lawrence, C. H.: Endocrinol. **12**:245, 1928.
130. Russell, D. S.; Evans, H., and Crooke, A. C.: Lancet **227**:210, 1934.
131. Rutishauser, E.: Deutsches Arch. f. klin. Med. **175**:640, 1933.
132. Schellong, F.: Klin. Wchnschr. **10**:100, 1931; **2**:53, 1932; Verhandl. d. deutsch. Gesellsch. f. Kreislauforsch. p. 176, 1933; Ztschr. f. Kreislauforsch. **25**:429, 1933.
133. Scheps, M.: Compt. rend. Soc. de biol. **115**:1367, 1369, 1934.
134. Schockaert, J. A., and Lambillon, J.: Compt. rend. Soc. de biol. **119**:1194, 1935.
135. Sharpey-Schafer, E.: The Endocrine Organs. Longmans. 1926.
136. Sokolow, D., and Gromow, L.: Vestnik Endokrinol. **4**:411, 1934.
137. Spark, C.: Arch. Pathol. **19**:473 (April) 1935.
138. Spiegel, E. A.: Klin. Wchnschr. **9**:1241 (July) 1930.
139. Spiegel, and Yaskin: Quoted by Spiegel.

140. Susman, W.: Brit. J. Surg. **22**:539 (Jan.) 1935.
141. Swan, W. G. A., and Stephenson, G. E.: Lancet **1**:372 (Feb. 16) 1935.
142. Teuchmer, F. R.: West. J. Surg. **43**:127 (March) 1935.
143. Theobald, G. W.: Clin. Sc. **1**:225 (Nov.) 1934.
144. Thompson, K. W., and Cushing, H.: Proc. Roy. Soc. London, Ser. B, **115**:88 (May) 1934.
145. Touchard, R.: Thèse Fac. Med. Toulouse, 1933.
146. Trendelenburg, P.: Ergebn. d. Physiol. **25**:364, 1926.
147. Tschaikowsky, W. K.: Arch. f. Gynäk. **150**:583, 1932.
148. Volhard, F.: Arch. f. exper. Pathol. u. Pharmakol. **167**:32, 1932.
149. Wang, G., and Richter, C. P.: Chinese J. Physiol. **2**:279, 1928.
150. Weber, F., and Parkes: Brit. J. Dermatol. **38**:1 (Jan.) 1926; Brit. M. J. **1**:935 (May 21) 1932.
151. Wieth Pedersen, G.: Hospitalstid. **74**:1231, 1931.
152. Wohl, M. G.; Moore, J. R., and Young, B. R.: Radiology **24**:53 (Jan.) 1935.
153. Wyman, L. C., and tum Suden, C.: Am. J. Physiol. **109**:115, 1934.
154. Yamashita, K.: Iber. Kurashishi Z. Hosp. **8**:179, 1933; in Ber. ges. Phys. **80**:98, 1934.
155. Yater, W. M.: Arch. Int. Med. **41**:883, 1928.

MERCURIN SUPPOSITORIES AS A DIURETIC IN THE TREATMENT OF EDEMA*

BY MARSHALL N. FULTON, M.D.†

IN the treatment of edema, particularly chronic or recurrent edema, diuretic drugs frequently are of great service. Of these the organic mercurial salts have come to be used extensively because of their effectiveness in increasing urine output and their relative freedom from toxic effects. Salyrgan (mersalyl) enjoys a widespread popularity and has been found to be effective even when given repeatedly over a long period of time.[1, 2] During the past few years another preparation, mercupurin, introduced in Europe under the name of novurit, combining both a mercurial salt and theophylline, has been given enthusiastic recognition.[3, 4, 5] The disadvantages in the use of these drugs are (1) that they must be given either by intravenous or intramuscular injection, (2) that by the former route they are liable to injure the vein or surrounding tissues, and by intramuscular administration are irritating and painful and (3) that their repeated use requires frequent attendance of doctor to patient, or of patient to doctor or clinic, which necessity often curtails their employment. If either drug or any other preparation equally effective could be administered by the patient, himself, under supervision, there would be a saving both in time and money and added convenience of no little measure.

It has been shown in certain European clinics that the mercurial component of mercupurin, the sodium salt of trimethylcyclopentane-diearboxylicacid-methoxy-mercuryhydroxide-allylamide, is effective as a diuretic when administered by rectum in suppository form.[6, 7, 8] This preparation has recently been introduced in this country under the name of mercurin suppositories. During the past eight months at the Peter Bent Brigham Hospital we have had the opportunity of using mercurin suppositories in twenty-five patients with edema.‡ They have been found to be an effective and safe diuretic, producing results comparable with those obtained by the intravenous injection of salyrgan or mercupurin. These results are published with the feeling that this preparation offers a distinct advance in diuretic therapy, particularly in the convenience it affords to both doctor and patient.

PLAN OF TREATMENT

All but five of the patients with whom this report deals had cardiac failure with edema. Most of them were observed for a time at bed rest on the hospital wards. Following a period of several days' observation to allow for adequate digitalization or a spontaneous diuresis, they were given one gram of ammonium chloride three or four times a day. This therapy, introduced by Keith and his associates[9], has been shown to enhance the action of mercurial diuretics by the mild degree of acidosis which it produces.[10] After two to four days of this régime, the patients were given the suppositories usually the first thing in the morning following a cleansing enema. Use of the suppositories or other diuretics was repeated at intervals of four to six days, the patients, meanwhile, continuing on a daily dosage of three or four grams of ammonium chloride.

Each suppository, made of cocoa butter base, contains 500 milligrams of the mercurial salt of mercupurin ($C_{14}H_{24}O_5NHgNa$) without any added theophylline. This is approximately five times the amount of mercury contained in one cc. of mercupurin or salyrgan.

RESULTS

The diuretic response to the suppositories was very satisfactory, comparing favorably with that observed after intravenous administration of mercurial salts. The increased urine flow began in one to three hours after the suppository was given and was passed, as a rule, by the end of twelve hours, so that the patients were not kept awake the following night voiding urine. Occasionally the increased urine flow lasted twenty-four hours or longer. That the absorption of the material by the rectal mucosa may occur very promptly was indicated by one patient who had a bowel movement twenty minutes after insertion of the suppository, yet who

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‡We wish to express our thanks to the Campbell Products, Inc., 79 Madison Avenue, New York, N. Y., for the suppositories used in this work.

passed three liters of urine in the next twenty-four hours. In only one instance did a patient fail to have a diuresis with the suppositories after responding satisfactorily to other diuretics. Conversely, both suppositories and parenterally administered mercurials failed to induce a significant diuresis in six of the patients on whom they were tried. A few individuals complained of slight rectal irritation and burning for fifteen to thirty minutes after the insertion of the suppository; more stoical ones made no complaint. One patient occasionally passed mucus in the stools on the day the suppository was administered. In no instance were toxic effects observed from use of this form of medication as manifested either in the patient's condition or by changes in his urine or kidney function tests. The suppositories have been used by patients at home with results quite as satisfactory as those observed in the hospital.

The results are indicated in table 1 which shows the maximum and average twenty-four hour urine volumes observed on the days the suppositories were used. For comparison, figures are given to show the urine volumes when salyrgan or mercupurin were administered, intravenously, to the same patients. These figures do not afford a close measure of the comparative diuretic potency of these several preparations, inasmuch as the first diuretic given on admission to the hospital often calls forth a much greater urine excretion than those given subsequently. The urine output in edematous patients is influenced markedly, among other things, by the extent of edema present at the time the diuretic is given. The figures do show, however, that the urine output observed after mercurin suppositories compared very favorably with that following salyrgan or mercupurin given intravenously.

TABLE 1

Patient	24-Hour Urine Volume with: Mercurin Suppositories		Salyrgan 1 cc. Intravenously		Salyrgan 2 cc. Intravenously	
	Maximum	Average	Maximum	Average	Maximum	Average
	cc.	cc.	cc.	cc.	cc.	cc.
M. McC.	4575	3490 (6)	2600	2350 (2)	4050	3750 (2)
N. G.	4550	3350 (8)	2800	2620 (3)	5700	4700 (4)
J. K.	4450	3825 (2)	3800	2830 (5)	—	—
L. H.	4350	—	—	—	—	—
E. P.	4050	2620 (14)	1450	1425 (2)	—	—
R. F.	3990	2920 (3)	—	—	—	—
L. H.	3800	—	—	—	4100	2875 (4)
J. Z.	3500	2840 (8)	1700	1375 (2)	3250	2480 (14)
L. W.	3500	2865 (15)	3500†	—	5500†	3775 (18)†
J. R.	3400	—	2400	—	5650	5525 (2)
J. L.	3050	2625 (2)	—	—	4600	—
J. S.	3000	2360 (4)	4100	2760 (7)	—	—
T. K.	3000	—	3500	—	5380	4240 (2)
L. C.	2800	2350 (2)	3250	—	—	—
			4100*	3950 (2)*	—	—
M. H.	2750	1880 (4)	3550*	2675 (4)*	3200*	2550 (3)*
O. R.	2500	2200 (2)	—	—	—	—
J. W.	2200	1770 (3)	3500	2810 (4)	3600	—
S. T.	1800	1500 (2)	1950	—	4000	2470 (5)
S. H.	1800	1450 (2)	—	—	—	—
H. M.	1600	1425 (2)	—	—	2500	2060 (6)
J. B.	1300	—	—	—	—	—
G. K.	1050	925 (2)	2600	1850 (2)	—	—
M. L.	1000	900 (2)	1300	—	—	—

*Mercupurin instead of Salyrgan given.

†Salyrgan given intramuscularly.

Figures in parentheses denote the number of times preparation was given.

Patient E. P. had subacute nephritis in the nephrotic stage. Patients H. M. and M. L. had cirrhosis of the liver. All the other patients had either chronic myocarditis or chronic valvular heart disease.

The response of two patients is shown in charts 1 and 2.

Chart 1 (Patient M. McC.) is from the record of a thirty-eight year old single female with chronic rheumatic valvular disease (aortic and mitral stenosis and insufficiency, possibly tricuspid insufficiency). She began having severe dyspnea in 1933, and developed ascites which first required tapping in July of that year. Until the time of the first admission shown in the chart (September, 1935) she had ten abdominal paracenteses for recurring ascites, the last three being in April, June, and August, 1935. During 1935, she found it necessary, in addition to the hospital admissions for tapping, to attend the out-patient clinic some thirty-five times for intravenous injection of diuretics. Theocin

given at home caused nausea and vomiting. Urea was only moderately successful in increasing the urine output. With the diureses afforded by the medication, as shown in the chart, it was possible for the patient to go from October 25 until mid January without tapping. Suppositories, administered by the patient at home during December and January, produced twenty-four hour urine volumes varying from 3100 to 4300 cc.

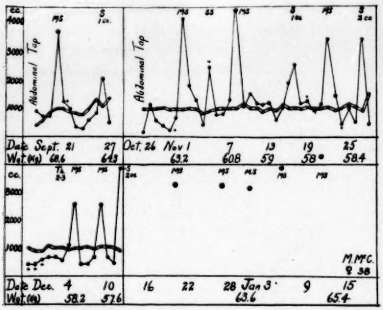
Abdominal Tap
Abdominal Tap
Date Sept. 21 27 Oct. 26 Nov 1 7 13 19 25
Wt (lbs) 626 643 632 608 59 58* 584
M.M.C.
Date Dec. 4 10 16 22 28 Jan 3 9 15
Wt (lbs) 582 576 636 654

CHART 1. (Patient M. McC.) Fluid intake and urine output during two hospital admissions between September 16 and December 12, and urine output following mercurin suppositories taken at home. In this and chart 2, circles represent the fluid intake; dots, the urine output; MS = mercurin suppository; S = salyrgan given intravenously; SS = suppository containing residue, after evaporation, of 2 cc. of salyrgan; Th. 2 = two doses of theocin, 0.3 Gm. each.

Chart 2 (Patient N. G.) shows the course during two hospital admissions of a forty-four year old male patient with chronic myocarditis and hypertension. In September, 1933, he had an attack of coronary thrombosis. Subsequent to this he had two admissions to the hospital because of angina pectoris and cardiac failure before total thyroidectomy was done in March, 1935. He was not greatly improved by this procedure, and on his fourth admission in October, 1935 (the first one shown in the chart) he exhibited marked cardiac failure with hydrothorax and edema of the extremities. He was, of course, given digitalis and ammonium chloride throughout the two admissions shown in the chart. Though it was not possible to rid the patient of his edema or to reduce his weight more than 11.2 kilograms, he was kept from the accumulation of massive anasarca by the repeated diureses. With the suppositories twenty-four hour urine volumes between 3000 and 4500 cc. were obtained repeatedly.

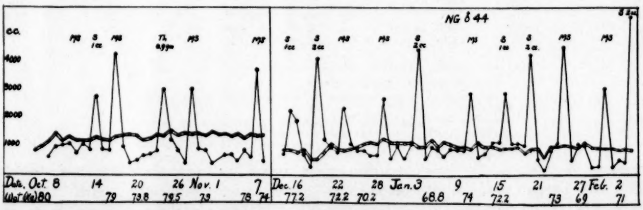

CHART 2. (Patient N. G.) Fluid intake and urine output during two hospital admissions between October 5, 1935 and February 4, 1936.

Patient E. P. (table 1) with the so-called nephrosis syndrome, having normal excretion of phthalein and no nitrogen retention, was given mercurin suppositories fourteen times during the course of four months with resulting diureses ranging from 1500 to 4000 cc. in twenty-four hours. During this time there was no evidence of added kidney damage from the mercury administered, and edema, while not abolished, was satisfactorily controlled. This case illustrates that certain selected patients with edema of renal origin, notably those with subacute or chronic nephritis who show normal ability in excreting phenolsulphonephthalein and nitrogen, may be given mercurial diuretics with safety.

Experience with the patient L. W. during the past ten months indicates the advantages incident to the use of the suppositories in patients with persistent edema who are well enough to be ambulatory. This patient, a forty-five year old Negro, has chronic myocarditis with recurrent ascites which has necessitated frequent abdominal taps, the last ones being done in June and September, 1935. Between June and November of that year, he made weekly trips to the out-patient clinic for the intramuscular injection of a mercurial diuretic. There was no other indication for such frequent visits. In November he was tried with mercurin suppositories with satisfactory results. For the past three months he has been able to extend the interval between visits to four weeks, taking a mercurin suppository each week at home with continued good response. During these three months his weight has remained constant. There have been no changes either in the urine examination or in the condition of the patient. Naturally, he prefers this form of therapy inasmuch as it abolishes the necessity of his frequent trips to the hospital.

The four patients having ascites and edema with cirrhosis of the liver, on whom the suppositories were tried, failed to respond with satisfactory diuresis. Only two of these (H. M. and M.L.) are noted in table 1. This is in keeping with the general experience at this hospital, that diuretics are much less effective in removing ascitic and edema fluid in patients with hepatic cirrhosis than in those with cardiac failure.[11]

COMMENT

The obvious advantage of this form of diuretic therapy is its simplicity and ease of administration. It does away with the clinical as well as the economic disadvantages of giving diuretics intravenously and intramuscularly. The same may be said of any of the diuretics given by

mouth, such as urea, theocin, metaphyllin or other drugs of the xanthine group. These other preparations, however, are not always well tolerated by patients, and do not effect in general so satisfactory an increase in urine output as that resulting from the mercurin suppositories. The latter, thus far in our experience, have produced diureses quite comparable to those obtained by parenterally administered mercurial salts.

It has been our experience with the suppositories, as with mercupurin and salyrgan, that the patients excrete more urine if an acid-forming salt such as ammonium chloride is given in daily dosage of three or four grams, either continuously or with occasional rest periods of several days between "courses". The suppositories have been repeated at intervals of four to six days according to the extent or persistence of edema.

The advantages obtaining from this method of administering diuretics afford a definite advance in the treatment of edema by diuretic drugs.

SUMMARY

Mercurin suppositories containing 500 milligrams of the mercurial salt of mercupurin, administered by rectum, have been found to cause diureses in edematous patients comparable with those observed after mercurial salts given intravenously.

No significant untoward or toxic effects occurred in twenty-five patients receiving from one to fifteen suppositories.

The simplicity of administration makes this form of therapy very suitable in the treatment of patients with edema in whom the use of diuretics is indicated.

REFERENCES

1. Wiseman, J. R.: The prolonged use of salyrgan as a diuretic: Report of 270 injections in five years in one case. J. A. M. A. 99:1114 (July 9) 1932.
2. Dixson, I. M.: Salyrgan: Its long-continued use in cardiac insufficiency with latent edema. New Eng. J. Med. 210:800 (April 12) 1934.
3. Fulton, M. N., and Bryan, A. H.: Some observations on the comparative effectiveness of mercurial diuretics with and without theophylline (mercupurin, salyrgan, etc.). J. Lab. & Clin. Med. 20:1252 (Sept.) 1935.
4. Crawford, J. H., and McDaniel, W. S.: Some observations on mercurial diuretics. Ann. Int. Med. 8:1266 (April) 1935.
5. DeGraff, A. C., Nadler, J. E., and Batterman, R. C.: Studies on the diuretic effect of mercupurin in man. Abstr., Am. Heart J. 10:832 (Aug.) 1935.
6. Parkinson, J., and Thomson, W. A. R.: A mercurial (novurit) suppository as a diuretic for cardiac oedema. Lancet. 1:16 (Jan. 4) 1936.
7. Dennig, H., and Kra e, E.: Diurese durch rektale Anwendung von Novurit. München. med. Wchnschr. 82:1865 (Nov. 22) 1935.
8. Epstein, T.: Neuere Untersuchungen über die rektale Anwendung von Quecksilber-diuretica. Heilkunde (Budapest) No. 37, 1935.
9. Keith, N. M., Barrier, C. W., and Whelan, M.: The diuretic action of ammonium chlorid and novasurol in cases of nephritis with edema. J. A. M. A. 85:799 (Sept. 12) 1925.
10. Ethridge, C. B., Myers, D. B., and Fulton, M. N.: The Modifying Effect of Various Inorganic Salts on the Diuretic Action of Salyrgan. Medical papers dedicated to Henry A. Christian, Baltimore, Waverly Press, 1936, p. 223. (To be published in Arch. Int. Med.)
11. Ethridge, C. B.; Myers, D. W., and Fulton, M. N.: Modifying effect of various inorganic salts on the diuretic action of salyrgan. Arch. Int. Med. 57:714 (April) 1936.

VERMONT STATE MEDICAL SOCIETY

THE BIOPSYCHIC APPROACH TO DISEASES OF THE MIND: ITS DEPENDENCE ON NEUROLOGY AND GENERAL MEDICINE*

BY FOSTER KENNEDY, M.D.†

NEUROPSYCHIATRY by its very nature must pervade all medicine, neurology must rest upon it, and must be the base of psychiatry. We who study these things must concern ourselves with the general field. You remember when Peter rested on the roof-top he saw a great sheet let down from Heaven, full of all manner of creeping and crawling things. Shrinking from them he heard a voice from on high saying, "Call nothing that I have created common or unclean."

In the past century neurologists were busy collecting, classifying and, as their often unappreciative colleagues would say, "labeling" specimens of neural disorders. Even today many physicians point at us an unwitting finger, thinking us an academic lot, full of wise saws but in the main signifying nothing. This view is long outgrown, far behind the realities of our employment. We have viewed and learned the flora on the ground's surface, tabulated and brought them into the scheme of law. Now is the task of digging into the ground to find the roots from which plants spring and of analyzing the soil—often heavy and seemingly unprofitable labor, but work which is the very stuff of medicine and on which will one day be established a true pathology of mind.

May we here examine a little the detail of this pretentious statement? For example, think of the rôle of focal infections in the production, often quickly, often after long intervals, of degeneration in the central nervous system. Abscessed teeth and chronic sepsis of the tonsils by perineural lymphogenous infections cause cervical spinal arachnoiditis with cord compression and slowly progressive paraplegia. Carbuncle of the neck, by lighting an almost instantaneous fuse, may cause an explosion in the upper spinal segments with transverse myelitis and quadriplegia. Diphtheritic sores of the hand have been shown to cause radiculitis and spinal paralysis of the affected arm; while the same diphtheritic sores on the thigh, throughout the British Forces in Mesopotamia, gave rise to cauda equina neuritis with double

*Read at the Annual Meeting of the Vermont State Medical Society at Rutland, October 18, 1935.

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dropped feet and paralysis of the sphincters. Kinnier Wilson has shown the part played by chronic lead poisoning in painters and cable layers in the later production of amyotrophic lateral sclerosis. If one neural poison can cause central cell degeneration in this manner, the same road of invasion is open to others whose nature still lies hidden from us.

Lately a woman was seen by us who gave a history of recurrent herpes zoster in the left second and third lumbar root skin areas of the left upper thigh. The painful eruption had appeared regularly for sixteen months in the first days of each menstrual period. She had consulted many physicians of the skin with slight symptomatic success. The clue to her condition was the discovery of an infected Bartholin cyst in the left labium which, aggravated at the period, caused an ascending inflammation of the appropriate roots and posterior spinal ganglia.

Again a man was seen who had extensive anterior horn muscular atrophy of the legs with fibrillary twitching, usually thought characteristic of progressive muscular atrophy. The absence of any signs of involvement of the cervical segments, however, caused us to suspect the existence of a local infecting focus. The cure of a chronic prostatic abscess, in this case, resulted in recovery of function in the lower spinal segments.

Last year a soldier had eight upper teeth removed at one time under local anesthesia. Three days later he began to have severe neck pains and occipital headache and, in two weeks, he died of meningitis. The road for bacterial invasion of the brain membranes had been opened through overconfidence in modern dentistry applied to infected tissues.

One may point out the dependence of some spinal cord degenerations on long-standing achylia gastrica which, in its turn, may depend upon a chronic cholecystitis.

A dozen years ago a violent epidemic of polyneuritis with many scores of fatalities was traced to streptococcal milk. The dependence of other inexplicable forms of neuritides is often found in nutritional deficiency, not due to inadequate diet but to inadequate assimilation through deterioration of function in the mucous membranes of the alimentary canal.

There is no need to pile Pelion on Ossa; we must realize that the causes of neural degenerations lie often in infections of other tissues. Within the lifetime of all here, paresis and tabes have been proved to be caused by lues and only by lues; but most of the older men as students were instructed that these two nervous diseases might come from overwork and exposure—presumably to the winds of Heaven! I was told as a student that paralysis agitans was "a neurosis" without organic basis. We know now its cellular pathology and much of its infective origin. Asthma was to me at college akin to the vapors of a still earlier day. Now we understand that its allergic etiology is due in great part to individual sensitiveness to specific proteins which may cause some forms of palsy, blindness, and various obscure cerebral illnesses.

So, we neurologists live in no ivory tower. We scurry over and delve in the fields of internal medicine and must also try to throw searchlights through the tenebrous fog of endocrinological fact and fable. So, too, we must deal with the aberrations of all the special senses. We must try to bare the causes of many cases of blindness, of discrete losses of vision, of diplopias and, often enough, of simulated disease. We must try to give a reason for subjective visual phenomena, like visual fits or the more complex hallucinations of men and things associated with disordered function in the temporosphenoidal lobe. We must know enough about sinus disease to distinguish between the pain caused by osteitis of the floor of an antrum and that of trigeminal neuralgia and between the localized headache due to pus in a sphenoidal sinus and a unilateral migraine. We neurologists must examine the ears ourselves and later secure skilled aid from the expert. We have to decide the significance of subjective ear noises and the significance of islands of lost hearing, to appraise labyrinthine efficiency and distinguish errors in semicircular canal mechanism from those of the cerebellar system. Errors in respiratory rhythm and palsies of the vocal cords, together with bulbar palsies and hysterical aphonias give us a link with the laryngologist. Thus the senses of taste, touch and smell, and the vagaries of speech all bring grist to our mill and we must grind thoroughly if we would make good bread.

We cannot busy ourselves with the spinal cord without acquaintance with its bony covering; nor can we deal with paralyzed members with no concern for the resources of the orthopedic surgeon in their cure. At times we can elucidate the cause of sciatic pain as being due to a tumor of the epiconus, not easily susceptible to spinal fusion, and aid by the diagnosis of dystonia musculorum in the orthopedic problem of the resultant disordered joint.

The palsies of the sphincters and the failure of the sexual reflex bring us into alliance and understanding with the genitourinary surgeon, but it is in the great problem of incurable pain that we can perhaps be of most assistance. Inoperable pelvic cancer, prostatic or uterine, may be made somewhat bearable by the operation of chordotomy, the division in the upper dorsal region of the tracts carrying pain impulses to the brain and consciousness. This operation, in

proper hands, is no more arduous to the patient than is an exploratory laparotomy or an appendectomy; it causes no motor palsy, no essential sensory loss, merely a transient sphincter disturbance and will secure the patient from most of the unpleasant features of morphine life. There is nothing to be said for the expectant treatment of bladder or womb cancer. When the diagnosis has been established and local treatment exhausted, chordotomy should be done before morphine addition has occurred.

All the specific fevers have their nervous concomitants, paralyses due to cerebral thromboses, neuritis, deliria, and psychoses. These latter, mark you, are the outcome of infection and fever. Is it not strange to us that a patient with pneumonia or typhus who, harassed by delusions of imminent destruction, throws himself from a window, is classified as delirious from fever, while the same psychic situation with no obvious intoxication may be called paranoiac, the organic pathology of which most psychiatrists deny? One patient is said to have a disease of the body, the other a disease of the mind. This is at once loose and dogmatic thinking. We must educe a pathology of mental disease through medicine; the effort to do so through philosophy and psychology has failed. They are useful till our knowledge of the body will have grown to larger stature. In therapeutics they deal well enough with symptoms, but a sharper sword is today being forged by medicine to deal with the nature of mental illness itself.

Often one hears a plea from the psychologist for the consideration of the human animal as a whole. We have often heard physiologists speaking of the cerebrum, the cortex, acting as a whole. I have never been quite able to understand clearly what is meant by the physiologist when he speaks of the cortex acting as a whole. Head uses the phrase in his writings. I have always thought it a very confusing term, but I think I do understand, or approximate to understanding, what is meant by a human being acting as a whole, in that the metazoic, multicellular animal functions in each act as uniquely, in as unified a manner, as does the unicellular animal. Each behavior, each act of behavior, is the resultant of the forces that are in the organism, so that I think one may properly speak of the human being as acting as a whole, which is far from being the same as feeling or thinking as a whole. Many lately have spoken rather adversely of Freud's philosophy, Freud's theory, as being a purely motivistic relation of human behavior. Now, unfortunately, those who speak decidedly on any side in this rather amorphous world get the reputation of being prejudiced.

Our antagonism, if it can be called antagonism—and it is only criticism—to psychoanalysis is not that it is wrong but that it is only true in part. It is one angle of view only. Our mind symbolizes anything we see; we see but one aspect at a time and that first and clearest that appeals to the consciousness of the observer. The important thing is to try to have more than one angle of vision; but the psychoanalyst seems to see like Polyphemus, with but a single eye and one cannot but feel that there is a certain belief in their circles that they have absorbed psychiatry. The psychoanalyst feels that only he is truly a psychiatrist and that unless one is a psychoanalyst one is not a psychiatrist, and that he who is not for them is against them. This is on the banner of all religions. They suggest that one has no right or power to have a notion or an idea of human personality in other terms than theirs. Shakespeare was not a psychoanalyst, Voltaire was not a psychoanalyst, George Moore and Thomas Hardy were not psychoanalysts, but I venture to say that these men knew more of the human spirit and the motivistic phenomena that prevail in the human heart than most of Freud's disciples. The great artists are perhaps the greatest of all psychiatrists. Their understanding may be better than our knowledge. So, I feel the Freudian contribution to be this: Freud has demonstrated that there is a phylogeny of personality. By that I mean that each of us is a microcosm of our race. From the egg to death we pass through stages in our body at least similar to those through which the whole race has passed. Freud has made it clear that in our emotion, in our striving, in the preponderance of this instinct over that at different periods of our lives, we have a like phylogeny of personality; that the child is a savage, that its sexual instinct emerges by gradual progression from a preoccupation with one orifice to a preoccupation with another. That is a true contribution to knowledge. Freud himself, however, has lately said that he is not sure whether it is a contribution to therapeutics but at least it does make it clear how our instincts developed inside the microcosm of each man's body. We have vestigial remains like gillslits and others like scatological tropisms, but we cannot describe the total body in terms of the one or the total personality in terms of the other.

This analysis of behavior has been, nevertheless, a great compensation against the materialism and dogma of the "cellular" epoch which perforce evolved in the nineteenth century. However, if we are to think solely in terms of this reversion to dualism, this ecclesiastical view of man, which has beset our minds and lamed our thoughts for two thousand years, if we are to think that such patterning and docketing constitute the whole of psychiatry, then,

I say, we are sinning against the Holy Ghost, the Holy Ghost of Medicine.

We must remember the plain facts of fever psychosis, the fact of glycosuria in shell-shocked soldiers. If we imagine each human being to be a single unswerving, unchanging uniformity against which stimuli are directed, and if we postulate that each such individual invariably reacts to stimuli in the same way as does every other individual, then we are saying something contrary, I am sure, to human experience and to common sense.

Individuals vary as much in their personalities and reactions as in their faces. They differ, as even Freud has stated, in their inherited endowments. I am not sure whether "inherited endowment" is an absolute fixed concept. I am even inclined to question the dogma that there is no such thing as the inheritance of acquired characteristics. Indeed, part of our trouble in this whole discussion is that we see the problem narrow and we see it short. We think in too small units of time. We cannot see the results of inheritance of acquired characteristics because of the paltry shortness of our lives and, because our eyes are fixed, our minds are too.

There is a good deal of evidence in the animal world that such transmission of acquired characteristics exists, that a defective germinal cell will produce a defective descendant and that the defective descendant will procreate a defect in his descendant. It has been done by an injection of pulverized lens tissue of rabbits into fowls whose serum thereafter put into pregnant rabbits produced creatures with defective eyes inherited to eight generations. If that can happen in the lower animals it may happen to us; only our nervous systems are so complex, they are so much more evolved, that we cannot see them in terms of our little lifetimes.

Good heredity and the care of the stock is the most important factor in the prevention of the psychotic state. Of course, psychogenic disease does exist. There are the results of great injury, great shock, but consider in this regard the results of the greatest disasters and the greatest emotions, consider the emotions of war. The statistics of the last war, which was a great laboratory for this investigation, show that while psychoneuroses were very frequent, in the tens of thousands, there was no increase of psychoses in the troops over those afflicting the same number of people in civil life. How do you account for that? If our psychoses are produced only by biological pressure how do you account for the absence of an epidemic of psychoses in the war? You cannot. Of course, the pressure of the herd, the pressure of the sex, the pressure of hunger all impinge on and mould, modify and direct, the growing organism. A man, who may be a potential homosexual, may be made a complete homosexual by experience, but I believe he must be nearly a complete homosexual to resist the normal trend of physiological living.

I dislike the new term "mechanistic approach". I think this word does its idea much less than justice. We do not think of using or advocating a mechanistic approach solely. What we advocate is that we should employ all our physiological knowledge, all our anatomical knowledge, all our social, our anthropological knowledge, our bacteriology, our histology, our morphology, bringing them in co-ordinated cohorts to find out the nature of the mind of man instead of limiting our approach by an arbitrary symbolistic theory. We should treat man as a dynamic and physiological whole.

Our attitude is more a biopsychic approach. After all, who would think of trying to discover the meaning of sight, of vision, without examining the eyeball? Nobody. If we should think of sight without any reference to the eye, without any reference to the physiology of the retina, with no reference to the brain tracts or to the ability of the cortex to gather up and differentiate sensations that come into it and to unify them, all purely in a physiological manner, we should know nothing of sight. Very well. What we would know of sight, lacking such consideration, would not be sight, but esthetics, visual esthetics, and we would be dwelling in this, too, as among the mysteries.

We all err in trying to explain the unknown by something equally unknown. We look up in the dictionary the word "vitality" and we find it means "zest"; we look up "zest" and find it means "vitality". If we do not know the meaning beforehand we may as well not open the book. All things may be viewed in several ways. The first chapter of Genesis is just as true as Edwin Clodd's "Story of Creation." We must believe that we cannot have intellect, dreams, or ecstasies without a fine inherited neuronic endowment. The strategic outlines and boundaries of mind are laid down by heredity, its tactical plan by social inheritance, by education and by the moulding pressures of sex, the herd and hunger. All, all may be destroyed by infection or by injury. In conclusion, we doctors have to remember that man is lowly in his beginning, agonized in his growing, most wonderfully and variously made in mechanism, and that there is in him a spirit that overleaps the stars.

CASE RECORDS
of the
MASSACHUSETTS GENERAL HOSPITAL

ANTE MORTEM AND POST MORTEM RECORDS AS USED IN WEEKLY CLINICAL-PATHOLOGIC EXERCISES

FOUNDED BY RICHARD C. CABOT, M.D.

TRACY B. MALLORY, M.D., *Editor*

CASE 22221

PRESENTATION OF CASE

A seventy-seven year old fisherman was admitted to a convalescent hospital complaining of swelling of the lower extremities.

Three weeks previous to admission he first noted some weakness which was associated with moderate difficulty in breathing. There was also slight dizziness and a gradually progressive edema of both feet and legs.

Thirty-five years prior to his entry the patient had had a carcinoma of the lower lip excised. One year later he returned with an ulcer of the lip which was thought to be a recurrence but which on section showed no evidence of malignancy. Twenty years before entry he was seen in the Out-Patient Department with a generalized skin rash, sores on his tongue and lips, and was found to have a strongly positive Wassermann test. Nine years later the Wassermann was still strongly positive. Six years before his final entry he returned to the hospital with a complaint of pain in the right side of his abdomen of three weeks' duration associated with nausea, vomiting, and occasional shooting pains radiating down into his genitalia and both legs. A huge mass was palpable in his right upper quadrant and shortly thereafter a transperitoneal nephrectomy for hypernephroma was done. At operation it was noted that the glands in the region of the renal pedicle were involved but were inextricable.

Physical examination showed a well-developed and nourished pallid elderly man. The lower lip was contracted and scarred. The heart sounds were distant and muffled in character. No murmurs were audible. The blood pressure was 140/80. The radial vessels were tortuous and sclerotic. The lungs were clear. There was a small ventral hernia noted. The scars of the two previous operations were not remarkable. There was tenderness in the right upper quadrant but no mass was palpable. There was pitting edema of both lower extremities and a large exostosis was felt protruding from the surgical neck of the humerus.

Examination of the urine showed a specific gravity of 1.014 with a slight trace of albumin. The sediment contained 30 white blood cells per high power field. The blood showed a red cell count of 3,000,000, with a hemoglobin of 39 per cent. The white cell count was 4,400, 68 per cent polymorphonuclears. A blood Wassermann test was negative.

The patient remained in the hospital for six months, during which time his edema persisted despite varied therapeutic measures. His temperature ranged between 98° and 99° and his pulse between 60 and 80. A hypochromic anemia which had been noted was improved by the administration of iron and liver. His general condition improved to such a point that during the sixth month he was allowed to return to his home for several one-week vacations. His edema, however, remained little improved despite digitalization. During the seventh month vague complaints of dyspepsia led to a gastrointestinal x-ray. The films showed a large polypoid filling defect in the anterior wall of the stomach measuring about two inches in diameter. Thereafter his condition remained essentially unchanged although he had occasional nocturnal epigastric discomfort, which was relieved by alkalies. During the tenth hospital month he developed chills, a temperature of 103°, and pain in the right side of his abdomen. Examination of the chest was recorded as being negative. There was some urinary frequency and burning dysuria. He was given fluids intravenously. A urine examination showed no change from the admission specimen. Thereafter he became progressively weaker, his temperature ranged between 100° and 103°, and the pain in his right upper abdomen persisted. He died about ten and a half months after entry, two weeks after the onset of his acute symptoms.

DIFFERENTIAL DIAGNOSIS

DR. FLETCHER H. COLBY: It seems apparent that neoplastic malignant disease is the chief consideration in this patient. This individual had cancers of two parts of the body, that of the lip thirty-five years before entry, and that of the kidney, six years before. The chief point to be determined, it seems to me, is whether the gastric tumor which was discovered three months before death is related to either of these other two neoplasms.

The high lights in the history are these: an elderly man with progressive and persistent edema of the lower extremities, weakness and anemia and the obvious presence of a large tumor of the stomach. There is no evidence of marked circulatory weakness to account for the edema. It is limited to the lower extremities. It did not recede with long periods of rest. Likewise there is no evidence of marked renal impairment, although one kidney was removed six years before; but the description of the terminal illness does not suggest uremia. The edema, then, would appear to be due to obstruction to

the return circulation in the large vessels. The cancer of the lip is dead and buried. That was thirty-five years ago and there has been no recurrence since. I do not believe it needs to be considered. A large malignant renal neoplasm was removed from this patient six years before. My compliments to the surgeon who did it. A transperitoneal nephrectomy in the first place, in the presence of such a large mass, is a difficult procedure. It was noted by the surgeon at that time that there were enlarged lymph nodes, presumably tumor-laden lymph nodes, in the region of the right renal pedicle. These probably were situated on the large vessels and it is reasonable to suppose that those large lymph nodes continued to grow larger and cause obstruction to or possible actual involvement of the large veins. Secondary tumor deposits from certain of the renal tumors grow very slowly. It is not uncommon to have recurrences five to twenty or more years after the removal of these malignant tumors called hypernephromas. They are all probably species of cancer. They most frequently, as you probably all know, metastasize to the lungs and to the bones. The exostosis of the humerus might be a secondary deposit, I do not know. There is only that to go on and frequently these tumors metastasize to bones and by choice to the long bones. There is no evidence of involvement of the lungs although such may easily be present.

Is the gastric tumor primary or secondary to the renal growth? Metastases from hypernephromas can involve any part of the body. It is unusual for them to involve the stomach. This might be an extension from the tumor in the region of the large vessels, actual tumor extension to the stomach; but if that were true I think we would expect to find a large palpable mass in the upper abdomen. Such was not present. The gastric tumor is described as polypoid in character. That sounds more like a tumor which came from the stomach itself than a metastatic nodule of tumor tissue or tumor that has extended to the stomach and involved it. I do not believe this individual is entirely free of his renal growth. It is reasonable that these lymph nodes which were discovered at the time of operation six years before have continued to grow larger and have caused obstruction to the large vessels either by pressure or by actual tumor extension. I believe that the gastric neoplasm is an independent one. That makes this individual have three different cancers. I think his liver probably is involved by the cancer and that would probably account for the pain in the right upper abdomen. I think in all likelihood he died of terminal pneumonia.

DR. TRACY B. MALLORY: Dr. O'Neil, you operated on this man. Will you tell us about it, please?

DR. RICHARD O'NEIL: I remember this patient. I saw him in consultation with the surgical service and at that time he had a large mass in the right upper quadrant. As I remember, there was no history of hematuria. When it is present of course it is a very significant element in renal diagnosis but it is not by any means constant, and it is not uncommon to see a renal tumor that does not have hematuria. Cystoscopy and pyelogram were made and were typical of renal tumor, and a transperitoneal nephrectomy was done. Incidentally, it is interesting to note that in looking over cases reported by Dr. Smith that the first time a pyelographic diagnosis of renal tumor was made in this hospital was in 1916, which seems extraordinary because pyelograms were being made some time before that.

The operation on this man was done under spinal anesthesia and the tumor removed transperitoneally, which is the best route for these large renal tumors. You can get better access to the pedicle. It was noted he had some glands which were not removed because they were adherent to the great vessels. The extraordinary thing is that this man had gone five years after an incomplete operation and had no deep x-ray therapy. He was seen by Dr. Simmons who suggested that he should have x-ray treatment. Dr. Holmes saw him and advised against it unless the man could come in and have a regular course of treatment, which he did not do.

In a series of twenty-six operative cases of hypernephroma reported from this hospital in 1925, one lived ten years, two eight years, one seven years, and one five years. In a series of thirty-four cases not operated on, the duration of life from the first symptom was in one case seven years, one five years, and one four years. So apparently some do as well without operation as with it. In a series reported by Dr. Hyman of New York, of forty-two cases, nine per cent lived five years, twenty per cent lived four years and twenty-six lived three years. In another series of twenty-five cases all died within seven years. In another series of Berg of Norway, of thirty-seven cases, seven lived five years. In these series the time of the appearance of the first symptom to the time of operation varies greatly—one case had hematuria for eleven years. He was operated on and lived for nine months. In contrast to this it might be interesting to say that I had a case four years ago in the Baker, a man thirty-two years old who had hematuria for one day only. He consulted his own physician that night. I cystoscoped him the next morning. At that time there was no hematuria, so a bilateral pyelogram was made which demonstrated a renal tumor. That is, the diagnosis was made within

twenty-four hours of the first occurrence of the symptom, which is very unusual. He had nephrectomy four days later. That is about as quick as you can do it. He was all right a year later.

I think in this case, as Dr. Colby said, that there were two different types of malignancy present but that the renal condition has something to do with his death.

DR. MALLORY: During the last two years of this patient's illness he was followed, not in this hospital, but in the Chelsea Marine Hospital. Dr. Dearing will tell us their impression.

DR. W. PALMER DEARING: As we saw him during this period of nine or ten months the striking thing was the one Dr. Colby pointed out, the edema of the lower extremities, which continued to be so intractable. It did improve as the anemia was treated and did improve a little with his digitalization, but at the same time there was no definite evidence of cardiac decompensation.

The other thing about his course was that two or three times he would flare up with febrile attacks for a few days and complain more of abdominal pain, then would get better. At no time could anything definite be felt in his abdomen though he was constantly tender in the right upper quadrant. When he finally died we felt that he probably had some infected metastases in the liver from the gastric tumor and a question arose as to what the old tumor that had been incompletely removed was doing, but we felt as Dr. Colby did that the stomach tumor was something different, another neoplasm.

CLINICAL DIAGNOSES

Carcinoma of the stomach.
Hepatic abscess.
Recurrence of hypernephroma?
Chronic myocarditis.
Exostosis of the right humerus.

DR. FLETCHER H. COLBY'S DIAGNOSES

Carcinoma of the stomach.
Recurrent carcinoma of the kidney with metastasis to the liver.

ANATOMIC DIAGNOSES

(Renal cell adenocarcinoma, right kidney.)
Operative scar: Nephrectomy, right.
Recurrence of the renal cell adenocarcinoma at the operative site with extension along the right spermatic vessels, the right renal vein and inferior vena cava.
Hepatic abscess.
Pulmonary abscess.
Pulmonary edema, bilateral.
Carcinoma of the stomach.
Multiple gastric polyps.
Pleuritis, chronic fibrous, bilateral.
Prostatic hyperplasia.
Trabeculation of the bladder.
Osteoarthritis, hypertrophic.
Exostosis of the right humerus.
Ventral hernia.
Decubitus ulcers.
(Syphilis).
Operative scar: Excision of epidermoid carcinoma of the lip.

PATHOLOGIC DISCUSSION

DR. MALLORY: The autopsy showed very close to what was predicted. He had a local recurrence of his hypernephroma at the site of the original incision and this tumor, as is so characteristic of hypernephromas as a group, had directly invaded the renal vein, had grown backward down the spermatic vein, had grown into the vena cava, and reached nearly up to the portion of the vena cava which passes through the liver. So that his edema was undoubtedly explained primarily on the physical basis of a tumor thrombus almost completely plugging the vena cava.

The stomach proved very interesting. It showed three separate polypoid tumors, two rather small ones along the lesser curvature, apparently not visualized by x-ray, which histologically were perfectly benign polyps, and a large one on the anterior surface near the greater curvature. Microscopically the major part of the large polyp closely resembled the two small ones, and appeared benign in character. There was one definite focus of malignant degeneration, however, such as we see from time to time in tumors of the stomach that evidently start as benign lesions.

The liver showed a fair-sized abscess in the right lobe, with no evidence that it was connected in any way with the tumor. It was about six or seven centimeters in diameter and there was a very small metastatic abscess in the lung, half a centimeter in diameter, which had nothing to do with his death. I should think death was probably due as much to sepsis from the liver abscess as any other single thing.

I think the case is interesting in pointing out one of the fallacies of the naïve era of medical statistics. It used to be taught that multiple cancers were a great rarity. The obvious reason for that is, of course, that the great majority of cancer patients died within a relatively short period from the first cancer that they developed and consequently very few of them lived long enough to have a chance to develop a second cancer. When adequate statistical correlations were made it has been possible to show, as Dr. Lund and various other people have done, that an individual who has had one cancer stands a very much better chance to develop second cancer than the laws of chance

would allow. There is undoubtedly such a thing as a tendency to neoplastic growth. This man had three separate malignant neoplasms. The lesion in the humerus turned out to be a benign exostosis and I think it is rather questionable whether that can be brought into the same category, but I feel reasonably sure if he had been able to live five years more he would have shown still other separate distinct cancers.

DR. O'NEIL: Any evidence of bone metastases?

DR. MALLORY: Nothing that we found. There is one point not mentioned in the physical examination that might have been a help to Dr. Colby. There was bilateral varicocele which would have been additional evidence in favor of thrombosis.

DR. GEORGE W. HOLMES: What about his liver abscess?

DR. MALLORY: We found nothing to suggest the origin.

CASE 22222

PRESENTATION OF CASE

A sixty-nine year old white housekeeper was admitted complaining of bleeding from the rectum.

The patient stated that for a number of years she had had a "delicate stomach" which was relieved by four sinus operations, the last of which was performed seven years ago. She remained comparatively well until about six months before entry, when she began to have vague colicky pains, occasionally on one side and then on the other side of the abdomen. These pains were associated with borborygmus, gaseous eructation, and the passage of flatus. For the last two months these attacks occurred several times a week without relation to meals and were not relieved by bowel movements. Her bowel habits were unchanged but the stools, although not diarrheic, were definitely looser than previously and were occasionally dark in color. Four weeks prior to admission she began to have gnawing epigastric pain which was relieved by food ingestion. Her appetite was increased but only for lettuce and such foods. More substantial material seemed to lie heavily in her stomach. There was no vomiting. Three days before coming to the hospital she passed about a pint of dark blood by rectum. Subsequently she passed similar material on two occasions during that day. She felt weak and on the day of entry began to vomit. She thought that she had lost some weight.

Physical examination showed a pale, thin, feeble, sick-looking woman suffering from nausea and vomiting during the examination. Slight tenderness was elicited over both maxillary sinuses. The mucous membranes were pallid. The heart was not enlarged and a soft systolic murmur was audible at the apex. The blood pressure was 160/80. The lungs were clear. The lower midabdomen was full and there was elastic balloon-like resistance in the right lower quadrant. To the right of the umbilicus there was a firm, slightly tender rounded mass, about four centimeters in diameter which seemed to move slightly with inspiration. Peristaltic sounds were slightly increased. No further findings were noted.

The temperature was 99°, the pulse 100. The respirations were 22.

Examination of the urine showed a specific gravity of 1.020 and a slight trace of albumin. The sediment was negative. The blood showed a red cell count of 3,900,000, with a hemoglobin of 50 per cent. The white cell count was 11,300, 89 per cent polymorphonuclears. There was considerable achromia, anisocytosis, and an occasional stippled red blood cell. The nonprotein nitrogen of the blood was 35 milligrams and the chlorides were 104. The serum protein was 5.2 milligrams per cent.

A portable flat film of the abdomen showed a moderate amount of gas in the bowel overlying the true pelvis and in the region of the cecum and descending colon. The cecum did not appear grossly dilated. An indefinite rounded area of density was seen superimposed above the region of the ascending colon, just above the crest of the right ilium. The diaphragm was low in position. Two days later another flat film showed the gas filled colon to be normal in size. The rounded areas of density, previously described over the crest of the right ilium, appeared to be within the bowel and had the appearance of a fecolith.

On the second hospital day the patient received a transfusion and two days later a laparotomy was performed.

DIFFERENTIAL DIAGNOSIS

DR. OLIVER COPE: The cause for this patient's entry to the hospital is intestinal obstruction. The problem lies in determining first the point of obstruction and secondly the cause. The first symptoms of obstruction started six months ago. Presumably they were intermittent until two months ago, when the frequency of the attacks of pain suggest that a chronic obstruction existed. Complete obstruction apparently occurred a short time before entry and was the immediate cause of her entering the hospital. Taking the history alone, the probability would be that the obstruction lies either high in the large intestine or low in the ileum. If the obstruction were either in the rectum or sigmoid, in other words low in the bowel, there would have been some change

in the bowel habits. The intermittent attacks of pain would have been accompanied by intermittent constipation. The lack of change of bowel habit is consistent however with obstruction on the right side of the colon or in the terminal ileum. The complete absence of change in bowel habit is strongly suggestive of ileal obstruction. The slight increase in softness of the bowel movement is consistent again with right colon or ileal obstruction. The fact that there was no frank diarrhea again suggests that the obstruction is in the ileum and that relatively normal bowel contents existed in the right side of the colon. Again, from the history, the obstruction is probably not high in the small intestine. Vomiting would have appeared much earlier and the patient would not have been able to eat so well as she has. In fact the lack of change in appetite suggests that the obstruction, if in the small intestine, must be low in the ileum. It is consistent with such an ileal obstruction as well as with large bowel obstruction.

I am unable to tie up the "delicate stomach" relieved by sinus operations with the diagnosis. The "delicate stomach" would fit well with an antecedent gallbladder disease, but it was apparently relieved seven years ago. I can think of no disease which would give sinus disease relieved for seven years and then give intestinal obstruction. Were there not the long interval of relief, diffuse diseases such as lymphoma, which may present a terminal intestinal obstruction, should otherwise be considered in the differential diagnosis. I am forced to omit the sinus trouble in the discussion.

The physical examination suggests two things of importance. In the first place a small, movable, firm mass in the right lower quadrant, and in the second place a large, boggy, balloon-like mass. This latter lying in the right lower quadrant presumably would be a dilated cecum, but the small mass if it were the cause of the obstruction should lie above it near the hepatic flexure. The fact that the small mass, which I presume is the cause of the obstruction, is differently placed suggests that it lies in the terminal ileum and that the boggy mass must be dilated small intestine.

The laboratory examination is significant. The blood examination is consistent with the recent loss of blood. From the history it is obvious that this loss of blood must have been from the bowel. The fact that the nonprotein nitrogen and the blood chlorides are well within normal limits suggests again that the obstruction if in the ileum must be low. If the obstruction were higher in the small intestine there would have been greater loss of water and salt with an elevation of the nonprotein nitrogen and a drop in the blood chloride. The low serum protein of 5.2 milligrams is consistent with hemorrhage. The x-ray helps and at the same time it is quite confusing. The second flat plate definitely excludes the large bowel as the origin of the obstruction. A normal sized gas-filled cecum places the obstruction in the small intestine. In the first plate a rounded area of density just above the right ileum, approximately where the small mass is described in the right lower quadrant, suggests that that mass is a large gall stone. A large gall stone in the terminal ileum is occasionally a cause of acute intestinal obstruction. In the cases that I have seen, however, no such long history of intestinal obstruction occurred. Once the gall stone had found its way into the small bowel there followed an acute episode of obstruction. I have also never seen bleeding as a complication of gall stone ileal obstruction. Presumably it might occur but the amount of bleeding which this patient had obviously had suggests an ulcerating area of longer duration than would have been produced by a gall stone. The second plate suggests that this mass is in the large bowel and not in the dilated bowel and therefore that it is below the point of obstruction. For these three reasons I dismiss a gall stone as the cause of the obstruction.

Hemorrhage from the small bowel with subsequent acute obstruction can be due to a Meckel's diverticulum, but the story of obstruction is of too long a duration. The patient is also of cancer age. If a Meckel's diverticulum is involved in this patient's disease I would go so far as to hazard the guess that it was a carcinoma of the diverticulum with hemorrhage and obstruction. Carcinoma is the most likely disease if one excludes lymphomas. I have never known a lymphoma to give ulceration and bleeding similar to that in this patient.

Carcinomas of the small intestine are very rare. Carcinomas of the large intestine are much more frequent. Carcinomas of the appendix itself which might produce obstruction to the terminal ileum are also rare. Neither a study of the patient nor the x-ray examination enables us to make a flatfooted localization of the process. Therefore, on the basis of probability, I believe this patient had a carcinoma of the ileocecal valve arising really from the large intestine but causing obstruction of the small bowel alone.

PREOPERATIVE DIAGNOSIS

Carcinoma of the right colon.

DR. OLIVER COPE'S DIAGNOSIS

Carcinoma of the ileocecal valve.

PATHOLOGIC DIAGNOSIS

Adenocarcinoma of the cecum, grade II.

Pathologic Discussion

Dr. Tracy B. Mallory: This patient was explored by Dr. Daland, who found very nearly what Dr. Cope had predicted. The main portion of the tumor was in the tip of the cecum, which was markedly contracted. The tumor had grown into the base of the appendix for a distance of about 2.5 centimeters. It had extended on the other side just to the margin of the ileocecal valve although anatomically this did not appear to be markedly narrowed. No evidences of metastases other than two small lymph nodes in the mesentery could be discovered, so a resection of the cecum, ascending colon and terminal ileum was done. The stump of the ileum was anastomosed to the transverse colon. Microscopic examination showed a well-differentiated adenocarcinoma and also proved that the palpable lymph nodes were free from metastasis and enlarged only by an inflammatory reaction. Following operation the patient did well and was discharged relieved three weeks after operation.

The New England
Journal of Medicine

SUCCESSOR TO
THE BOSTON MEDICAL AND SURGICAL JOURNAL

Established in 1828

Published by THE MASSACHUSETTS MEDICAL SOCIETY under the jurisdiction of the

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SUBSCRIPTION TERMS: *$6.00 per year in advance, postage paid for the United States, Canada $7.04 per year, $8.52 per year for all foreign countries belonging to the Postal Union.*

Material for early publication should be received not later than noon on Saturday. Orders for reprints must be sent to the Journal office, 8 Fenway.

The Journal does not hold itself responsible for statements made by any contributor.

Communications should be addressed to The New England Journal of Medicine, 8 Fenway, Boston, Mass.

THE INCREASE IN INCIDENCE OF DIABETES MELLITUS

IT is true that diabetes has been increasing and it is also true that the highest incidence of diabetes is in the United States. However, there are several factors which are often overlooked when startling statistics of this nature are published. Thus, in a recent compilation upon The Diabetes Record of 1934[1] we read that the death rate increased from 18.3 per 100,000 in 113 American cities in 1925 to 25.4 per 100,000 in 169 cities in 1934. As a matter of fact, the death rate from diabetes in the Original Registration States increased from 20.4 in 1920 to 28.8 in 1934 or 41 per cent. The corresponding figures for the Registration States of 1920 are 16.1 and 24.1 or 50 per cent. Now it happens that elsewhere in the world, where the rates have been much lower, the percentage increases have been much more rapid. Thus, in England and Wales in 1920 the rate was 10 and in 1934 16.0 per 100,000 and the increase, therefore, was 60 per cent. In Scotland in 1924 it was 10 per 100,000 but in 1934 15 per 100,000, or an increase of 50 per cent. In Italy in 1920 the rate was 4.5, but in 1934 it was 9.5 per 100,000 or an increase of 111 per cent. In Montreal in 1920 the rate was 12 and in 1934 18.7 or an increase of 56 per cent. Consequently, although the incidence of diabetes is increasing rapidly both in the United States as a whole and in its cities, the statistical increases are outdistanced in some other countries and cities and are gradually approaching the United States level.

In estimating the statistical evidence of diabetes in various parts of the world one must always bear in mind the accuracy with which the data are collected. Thus, in Canada, statistics show in 1934 the rate to be 12.2 per 100,000 for the whole country, whereas for Montreal 18.7 and for Toronto 16.6. Naturally the question arises as to whether in the rural areas in Canada diabetes is as assiduously sought for and diagnosed as in the urban areas and the same thought arises regarding rates in the rural and urban areas of the United States and in different sections of the country.

Other factors likewise must be borne in mind. Diabetes is a disease of middle age and adult life. The older the population the more diabetes can be expected and it is not strange that in New England the diabetes death rate per 100,000 for 1930 was 24.4, the Middle Atlantic States 25.5, East and West North Central States 21.4 and 20.6 respectively and Mountain States 13.3 per 100,000. Whereas the population of Vermont is small, and therefore not quite suitable for comparison, the rate varied between 29.4 per 100,000 in 1933 and 38.5 per 100,000 in 1934. In Russia according to a recent announcement in the daily press, 46 per cent of the population had been born since 1917 and therefore were nineteen years of age or less. In Massachusetts only 35 per cent of the population in 1930 was under twenty years of age.

The Vermont figures also bring up another fact of importance in evaluating the significance of incidence. Thus, there were only 106 deaths in 1933 and 139 deaths in 1934, producing changes in rates from 29.4 to 38.5 per 100,000 respectively. Obviously when dealing with such small numbers there is opportunity for misinterpretation of the facts. Even in a city as large as Boston the deaths changed from 331 in 1934 to less than 300 in 1935. The rate for 1934 was 42.3 per 100,000.

Other factors are of consequence, racial, urban versus rural types of population, environmental conditions particularly those leading to obesity due either to ease in securing food or reduction in necessity for muscular work. These conditions cannot be entered into here. They have been considered in detail elsewhere.[2]

The incidence of diabetes is rising, but in general it is increasing now more rapidly in

some other countries than in the United States. The age of the population is a great factor. Two-thirds of all cases of diabetes originate after the age of forty. Consequently, the per cent of the population above forty is important. Thus, in the United States in 1900 23.4 per cent of the population was above the age of forty, whereas 29.4 per cent in 1930. In 1845 in Boston, 80 per cent of the population died under forty years of age, but in Massachusetts in 1935, 80 per cent of the population died above the age of forty years. The increase of diabetes in the United States due to ageing of the population can be expected to go on until the average age of all deaths advances from its present level of 48.7 years to nearly fifty-five years, because this represents about the maximum age incidence for the onset of diabetes. It is true that in the United States the average age at death has advanced nearly one year for each two years (actually from 26.9 to 48.7 years) between 1880 and 1930 but it is logical to infer that increases of longevity and of diabetes in the future will proceed at a much slower pace. However, if one accepts the figures from Thompson and Whelpton's[3] book on "Population Trends in the United States" it is evident that the basis for further advances in the number of diabetics will continue for another generation. Thus, in 1900 17.8 per cent of the population was forty-five years of age and over and 4.1 per cent sixty-five years and over. In 1930 these figures were respectively 22.9 and 5.4 per cent, but it is calculated that by 1960 they will rise to 32.6 for forty-five years and above and 9.8 for sixty-five years and over.

REFERENCES

1. Hoffman, Frederick L.: The Spectator, October 31, 1935.
2. Joslin, E. P.; Dublin, L. I., and Marks, H. H.: Studies in diabetes mellitus; interpretation of variations in diabetes incidence. Am. J. M. Sc. **189**:163 (Feb.) 1935.
3. Thompson, W. S., and Whelpton, P. K.: Population Trends in the United States. McGraw-Hill.

THE EFFECT OF RADIATION ON MALIGNANT TUMORS

A CONTROVERSY as long standing as the application of radiotherapy to malignant disease is still unsettled as to the relative importance of the effect of radiation on tumor cells and on the stroma of the tumor and the supporting structures. Most experimental work has centered about the effect of radiation directly on the tumor cell. The work of the French school established the principle that actively proliferating tissues are peculiarly radiosensitive. With this so-called "law of Bergonié and Tribondeau" as a starting point, much attention has been paid to the effects on mitosis, with rather contradictory results owing to the variety of cells and the variety of types of radiation used. In general, the prophase of mitosis is considered the most easily injured.

The one finding on which all experimenters agree is that in any type of tissue, no matter how homogeneous it may appear, whether in the body or growing in tissue culture, the cells fail to respond identically to the radiation. A portion of this different response may be explained by variation in age of the cell, but it must also be influenced by inherent physiological differences in the various cells, irrespective of their age.

We are accustomed to speak of certain tumors as radiosensitive, in view of their marked regression after irradiation. On the other hand, after a satisfactory initial response, the same tumors, once they have recurred, fail to respond anywhere near so favorably, or indeed may not respond at all to the same dosage which gave good results the first time. In spite of the fact that the tumor has changed from radiosensitive to radioresistant, there is no demonstrable difference in the appearance of the tumor cell.

In this regard it is interesting to note that Strangeways and Hopwood found that even in irradiation of cells in tissue culture 100 erythema doses failed to kill every cell in the culture. This amount of x-ray dosage is, of course, far more than any human being could stand. A similar amount of radiation from radium was required to kill all the cells in tissue culture, as is demonstrated in the experiment of Speare.

A most interesting point is that there is a threshold of intensity below which no effect is obtained, no matter how long the radiation may be applied. In other words, even though a dosage of 500 mg. hrs. of radium be given, if the source be of very low intensity practically no effect would be obtained, whereas with a source of greater intensity a marked effect would be obtained.

Study of the histology of x-ray burns led Wolbach and Porter over twenty years ago to emphasize the importance of the effect of irradiation on the supporting tissues. This has been recognized clinically for a considerable period, one of the most striking examples being in the varying response of tumors of the same type according to the position in which they occur. Thus, basal cell cancers of the skin which normally respond well to irradiation when overlying connective tissue or muscle, respond poorly when overlying fat and even more poorly when invading cartilage or bone.

Histologic study of irradiated tumors showed two definite types of effect: an immediate effect on the tumor cell itself, in part exerted on cells in mitosis at the time of irradiation and in part, though to a lesser degree, on the other cells of the tumor. Subsequent to this immediate effect, a delayed effect on the vessels and on the subcutaneous tissue and the connective tissue of the stroma becomes increasingly important.

Thus we may well regard the radiation effect on a given tumor as the summation of the effect on tumor cells in mitosis, on resting tumor cells, on the vascular supply and on the connective tissue of the stroma and the surrounding tissues. That a dosage of x-ray or radium will destroy a tumor in the body when it would be insufficient to destroy the cells of that tumor growing in tissue culture shows that there is more than a simple destructive effect on the tumor cells themselves. There must be a secondary effect on the surrounding tissues which leads to the formation of a definitely unfavorable environment for the further development of the tumor cells.

"DEBUNKING" THE SURE CURES

PROFESSOR E. V. McCollum of Johns Hopkins University in addressing the Kings County Medical Society of Brooklyn, according to our learned contemporary, the *New York Times*, urged the medical profession to forestall the extravagant claims of retailers for the qualities of their medicinal preparations by thoroughly investigating all important new scientific discoveries.

Dr. McCollum has added greatly to our knowledge of the vitamins, and is consequently anxious that information which is practically applied should be approximately correct. While conceding that the secretory powers of mucous glands decrease for lack of vitamin A, and that the secretions of those glands contain an antibacterial substance, he sought to dispel the widespread belief that substances rich in vitamin A can prevent infectious diseases. Little if any improvement has been found in the incidence of common colds despite the regular ingestion of cod liver oil, although colds in the cod liver oil groups seem to be milder than in those not so indulging themselves. Vitamin A, however, he considers to be very important to the newly born, and its ingestion should be started early to prevent the cracking of teeth enamel and permanent injury to the tooth structure.

Vitamin B-1 is considered by Dr. McCollum to be highly important to the infant, and since milk is relatively poor in this substance, it should be added early to the infant dietary in the form of yeast extracts or other concentrates. Vitamin B-1 has also been found of value to chronic alcoholics, presumably on account of its anti-neuritic properties.

No fairer field for commercial exploitation has been found than that afforded the vitamins, but the success or failure of this exploitation, as Dr. McCollum indicates, is largely in the hands of the medical profession.

THE CANVASS OF CHRONIC AND DISABLING ILLNESS

IN a letter* to the Secretary of the Massachusetts Medical Society, Dr. L. R. Thompson, Acting Surgeon General of the United States Public Health Service, makes public the plan for securing the co-operation of physicians in the accumulation of accurate data relating to the incidence of chronic and disabling illness.

This means that, as cases of illness of these types are found by the investigators, the attending physicians will fill out and sign blank forms, setting forth the diagnosis in each case which the doctor has attended. For this service a fee of twenty-five cents will be paid.

This movement is commendable and should receive the effective support of the medical profession even though the service entailed may not be adequately remunerated.

If this plan is efficiently carried out, a great deal of valuable information will be at the disposal of the Public Health Service and should be the basis for constructive measures in dealing with the problems involved.

We hope that the medical profession will cooperate in this movement.

*See page 1112.

THIS WEEK'S ISSUE

CONTAINS articles by the following named authors:

JOSLIN, ELLIOTT P. B.A., M.A., M.D. Harvard University Medical School 1895. Medical Director, George F. Baker Clinic, New England Deaconess Hospital. Address: 81 Bay State Road, Boston, Mass. Associated with him are

ROOT, HOWARD F. A.B., M.D. Harvard University Medical School 1919. Physician to the New England Deaconess Hospital. Address: 81 Bay State Road, Boston, Mass. And

MARBLE, ALEXANDER. A.B., A.M., M.D. Harvard University Medical School 1927. Physician to the New England Deaconess Hospital. Address: 81 Bay State Road, Boston, Mass. And

WHITE, PRISCILLA. M.D. Tufts College Medical School 1923. Physician to the New England Deaconess Hospital. Address: 81 Bay State Road, Boston, Mass. And

JOSLIN, ALLEN P. M.D. Tufts College Medical School 1932. Address: 81 Bay State Road, Boston, Mass. And

LYNCH, GEORGE W. M.D. Harvard University Medical School 1933. Address: 81 Bay State Road, Boston, Mass. Their subject is Protamine Insulin. Page 1079.

HOUSSAY, BERNARDO A. M.D. For information see This Week's Issue, page 946, issue of May 7. His subject is Hypophysis and Blood

Pressure. Page 1086. Address: University of Buenos Aires, Buenos Aires, Argentina, S. A.

FULTON, MARSHALL N. Ph.B., B.A., M.D. Johns Hopkins University School of Medicine 1925. Physician, Peter Bent Brigham Hospital. Instructor in Medicine, Harvard University Medical School. His subject is Mercurin Suppositories as a Diuretic in the Treatment of Edema. Page 1092. Address: Peter Bent Brigham Hospital, Boston, Mass.

KENNEDY, FOSTER. M.D. National University of Ireland 1906. F.R.S. (Edin.) Professor of Clinical Neurology, Cornell University Medical College. Director, Department of Neurology, Bellevue Hospital, New York City. His subject is The Biopsychic Approach to Diseases of the Mind: Its Dependence on Neurology and General Medicine. Page 1095. Address: Bellevue Hospital, New York City.

The Massachusetts Medical Society

ANNUAL MEETING OF THE COUNCIL

The annual meeting of the Council will be held in the Ballroom of the Hotel Kimball, Springfield, on Tuesday, June 9, 1936, at 10:30 o'clock.

Please note the change of time.

Business:

1. Reading record of last meeting in abstract.
2. Nominating Committee retire to deliberate.
3. Report of Committee on Membership and Finance.
4. Reports of committees to consider petitions for restoration to the privileges of fellowship and new committees to be appointed.
5. Report of the Treasurer.
6. Reports of Standing Committees and Special Committees.
7. Election of Officers and Orator by ballot.
8. Appointment of committees for ensuing year, both Standing and Special.
9. Incidental business.

ALEXANDER S. BEGG, *Secretary.*

Boston.

Councilors are asked to sign one of the two attendance books before the meeting.

The Cotting Luncheon will be served immediately after the meeting.

SECTION OF OBSTETRICS AND GYNECOLOGY*

C. J. KICKHAM, M.D., *Chairman*, 524 Commonwealth Ave., Boston, Mass.
R. S. TITUS, M.D., *Secretary*, 472 Commonwealth Ave., Boston, Mass.

BRIGHT'S DISEASE IN PREGNANCY

During pregnancy certain kidney complications often occur. The presence of kidney disease before pregnancy may make it either impossible for the patient to give birth to children or inadvisable to make the attempt. Furthermore, the occurrence of kidney complications during pregnancy may and frequently does cause loss of life either to the mother or to the unborn child or perhaps to both. It is extremely important, therefore, both for the patient and for the physician to know something of what has gone on before pregnancy and a great deal of what is going on during it. For the purpose of this discussion we may classify the complications which involve or may involve the problem of nephritis as follows: (a) a group of complications spoken of as toxemia of pregnancy; a group that includes mild toxemia, sometimes designated as pre-eclampsia, and severe toxemia, which is termed eclampsia and which is always accompanied by convulsions; (b) a group of complications depending upon pre-existing Bright's disease or hypertension or on both; (c) pyelitis.

Toxemia of pregnancy probably has nothing much to do with any previous kidney disease. Its cause is really unknown. It is accompanied by hypertension, albuminuria and evidence of some disturbance of kidney and liver function. All of these signs and symptoms generally disappear as soon as pregnancy ends. Numerous attempts have been made to differentiate the toxemias of pregnancy and chronic nephritis and to demonstrate the return of function of the kidneys acutely damaged by severe toxemia or eclampsia. It has been demonstrated that ordinary procedures such as blood chemical studies, the phenolsulphonephthalein test and urine concentration test do not help differentiate chronic nephritis and acute toxemias. Recently the urea clearance test has been used for such a differential study. It was found that the results of this test checked up well with the clinical diagnosis, with only a few exceptions, and that the test gave normal readings in mild toxemias, decreased readings in severe toxemia or eclampsia and that the readings were definitely low with a high degree of consistency in chronic nephritis. Whether one can reclassify cases which ordinarily fall in the toxemia group

*This is the last of the series of short selected articles by members of the Section until Fall.
Comments and questions by subscribers are solicited and will be discussed by members of the Section.

as a result of urea clearance studies, can only be determined by following such cases over a long period of time.

The problem of pre-existing Bright's disease is naturally one of careful diagnosis. Severe Bright's disease hardly need be discussed for the patient is so ill that pregnancy generally is not to be considered and the chances of obtaining a live baby are so remote as to make the attempt questionable. On the other hand, mild Bright's disease may exist without the patient's knowledge and definite signs and symptoms may not occur until the kidney begins to demonstrate the strain of advancing pregnancy. Obviously, in mild cases, diagnosis of the condition before pregnancy is contemplated is the important point. The above statements apply to any case of pregnancy, but perhaps more particularly to those cases that have suffered some form of toxemia in the course of previous pregnancies. In other words, physicians are constantly confronted with the question of whether it is safe to allow a patient with a previous history of toxemia to become pregnant again.

The diagnosis of nephritis is not easy. In addition to a careful history and physical examination and careful examinations of repeated single urine specimens, such function tests as the fifteen minute phenolsulphonephthalein and the urea concentration tests are frequently necessary. This is especially true in those cases where there is any question of a previous nephritis or where there is a history of previous toxemia or repeated attacks of pyelitis. It is possible that the urea clearance test should be included in this diagnostic study, but the test is too difficult to be practical and furthermore, the results are not so clear-cut as claimed originally.

The difficulty with the problem is that all of the known diagnostic procedures may be used and all may give absolutely normal results and yet the problem may remain unsettled. The point is that there is no test which will indicate the type of response which the kidney will make to some future strain. Not only is this true, but the nature of the problem itself is such as to increase the difficulties for all concerned. For example, we know that so-called essential hypertension exists in various grades from mild to severe and that the grade depends upon the degree of vascular damage. We also know that in the mild grade frequently no evidence of kidney involvement can be determined and yet this mild grade may at any time shift into a more severe type. A condition like toxemia of pregnancy constitutes a vascular insult from which the patient may entirely recover. We do not know the cause of the toxemia but when we consider the problem of a second pregnancy we must remember that two of the factors which had something to do with the first attack are still present, namely, the type of the individual and the pregnancy. And in addition there is the question of residual damage to the kidney undetermined by any test now available.

The problem of the existence of a mild degree of Bright's disease in its relation to the question of pregnancy still remains unsettled. This is due to the fact that our methods of examination are not sufficiently delicate and that we have no method of determining the nature of kidney response to some future strain. Given a history of previous toxemia or repeated attacks of pyelitis or previous hypertension, careful diagnostic studies should be made before pregnancy is contemplated but, even after all this has been done, it is frequently necessary to settle the problem on the basis of clinical judgment with the full realization that one can never be certain what may or may not happen.

ADDITIONAL EXHIBITS AT THE ANNUAL MEETING

The Committee of Arrangements is pleased to announce that since the last issue of the *Journal*, it has secured two additional Scientific Exhibits, that were shown at the recent American Medical Association Meeting in Kansas City.

These two exhibits will be placed on the Lower Floor of the Auditorium, just outside the Lower Section Room. They consist of the following:

Booths A, B, C and D—

Diabetes, with Special Reference to the Use of Protamine Insulin.

1. Diabetic Coma.
2. Protamine Insulin.
3. Diabetic Surgery.
4. Diabetic Statistics.

From the George F. Baker Clinic, New England Deaconess Hospital, Boston and the Metropolitan Life Insurance Co., New York City.

Booths E and F—

Roentgenologic Study of the Heart. A Series of Mechanical Models.

From the Robert Dawson Evans Department for Clinical Research and Preventive Medicine, Massachusetts Memorial Hospitals.

By George Levene and Henry H. Lerner, Boston.

Booths G, H and I—

Moving Pictures.

The Technique of Roentgenologic Study of the Heart.

From the Robert Dawson Evans Department for Clinical Research and Preventive Medicine, Massachusetts Memorial Hospitals.

By George Levene and Henry H. Lerner, Boston.

CHANGE IN THE LADIES' PROGRAM

As a result of the flood, it is not possible for the ladies to have their tea at the Old New England Village as was originally planned. In place of this the Committee has arranged for a tea on Monday, June 8, at the George Walter Vincent Smith Art Gallery, 222 State Street, Springfield. Bus leaves Hotel Kimball at 2:45 P.M.

HOW TO REACH THE SPRINGFIELD COUNTRY CLUB

A BUS will leave Hotel Kimball, Monday, June 8, at 3:45 P.M. Members driving their own cars, cross the Connecticut River on the Memorial Bridge, turn right on leaving bridge, toward Holyoke. The club is about a mile from the bridge on the left side of the street.

MISCELLANY

THE CONTRIBUTION OF THE MEDICAL PROFESSION TO SPRINGFIELD'S TERCENTENARY CELEBRATION

The general committee of physicians consists of a representative from the staff of every hospital in Springfield and a representative from every medical club or society. Following several meetings during which the final plans were formulated, a subcommittee was organized. This committee has been busy in developing the first event of the Medical Profession's observance. It consists of Dr. Arthur J. Horrigan, Dr. Mary Burke, Dr. Charles Jurist, Dr. James A. Seaman and Dr. George L. Schadt, Chairman.

The Medical Profession's observance of the Tercentenary consisted of three parts. The first event was on Monday evening, May 18. On that day the committee entertained Dr. Henry E. Sigerist, Director of the Institute of the History of Medicine of The Johns Hopkins University, who delivered the main address at the evening meeting. During the afternoon a number of the local doctors with Dr. Sigerist made a pilgrimage to the grave of Dr. John Leonard, the first doctor who practiced in Springfield. Dr. Leonard probably arrived some time during the first third of the 18th century, or about 1736. Though little is known with reference to him, whence he came or from what school he received his degree, we know he died here on November 28, 1744, in his 69th year and lies buried in the Old Agawam cemetery which is in the town of Agawam directly across the river from Springfield. The doctors placed on the grave of John Leonard a wreath as a token of the local profession's respect and remembrance.

At 6:30 that evening, Dr. Sigerist was tendered a complimentary dinner at the Hotel Stonehaven by the physicians of the city.

At 8:30, an open meeting was held in the new auditorium of the Springfield Technical High School. As mentioned above, Dr. Sigerist delivered the main address of the evening entitled: "The Development of Medicine and Its Trends in the United States, 1636-1936."

This period, as you will note, covers the years of our city.

The second phase of the Medical Profession's Observance of the Tercentenary is the development of a medical exhibit sponsored by the Hampden District Medical Society during the meeting of the State Society at the Springfield Auditorium on June 8, 9, and 10. The committee in charge of this exhibit consists of Dr. Garry deN. Hough, Dr. James M. Smead, Dr. Fred H. Allen of Holyoke, Dr. Archibald J. Douglas of Westfield, and Dr. George L. Schadt as chairman. The committee hopes to present an exceedingly interesting exhibit.

As part of the exhibit there will be shown for the first time a series of six panels done in oil by a well-known local artist depicting the development of the doctor in fifty-year periods from 1636 to 1936. The artist is already at work on these panels and they will, undoubtedly, develop much interest among the members of the Society.

The final event in our program will take place in the fall when the series of six panels mentioned above will be presented to the Springfield Academy of Medicine by the families, friends and medical societies as a memorial to a number of physicians whose contributions to the life of their city were of outstanding significance. There will be placed on the walls of the Academy a bronze plaque listing the names of these gentlemen.

PHYSICIANS CERTIFIED AS QUALIFIED PSYCHIATRISTS

In our issue of May 7, on page 956, under the title Certification of Massachusetts Psychiatrists, were listed twenty-six physicians certified by the American Board of Psychiatry and Neurology as qualified to practice this specialty.

In our issue of May 14, the statement was made that Dr. Riley H. Guthrie was also certified as a qualified psychiatrist.

Other Massachusetts physicians certified are: Dr. Gerald F. Houser, Dr. Frank E. Leslie, Dr. Henry R. Viets, Dr. W. Franklin Wood, Dr. Hiram H. Merritt, Jr., Dr. Tracy J. Putnam, Dr. M. Ralph Kaufman and Dr. Kenneth J. Tillotson.

AN ADDRESS BY DR. WALTER B. CANNON

On April 29, 1936, Dr. Walter B. Cannon, George Higginson Professor of Physiology at the Harvard Medical School, delivered an address on "Sensitization of Denervated Structures" at the seventy-eighth meeting of the Maryland Biological Society of Baltimore.—*Science.*

COMPARISON OF DISEASE INCIDENCE IN CONNECTICUT WITH 1935 AND SEVEN YEAR AVERAGE

MONTH ENDING APRIL 25, 1936

Diseases	1936 Week ending Apr. 4	1936 Week ending Apr. 11	1936 Week ending Apr. 18	1936 Week ending Apr. 25	Average cases reported for week corresponding to Apr. 25 for past seven years	1935 Week ending Apr. 6	1935 Week ending Apr. 13	1935 Week ending Apr. 20	1935 Week ending Apr. 27
Amebiasis	—	—	—	—	—	—	1	—	—
Chickenpox	71	84	91	135	103	123	116	123	137
Conjunctivitis Infectious	9	3	6	—	4	7	12	6	—
Diphtheria	1	3	2	1	12	4	5	2	2
Encephalitis Epidemic	1	—	—	—	—	—	—	—	—
German Measles	330	184	269	89	40	93	125	149	222
Influenza	24	3	6	4	6	5	7	6	8
Malaria	—	—	—	1	—	—	—	—	—
Measles	50	91	104	109	310	1191	1779	1065	1263
Meningococcus Meningitis	2	4	—	1	2	1	2	1	—
Mumps	73	43	132	117	93	67	84	91	53
Paratyphoid Fever	—	—	2	—	—	—	—	—	—
Pneumonia (Broncho)	27	24	30	22	32	34	34	25	33
Pneumonia (Lobar)	31	33	57	36	41	46	58	44	43
Poliomyelitis	—	—	—	—	—	1	—	—	—
Scarlet Fever	102	47	63	57	83	130	105	110	76
Smallpox	—	—	—	—	2	—	—	—	—
Streptococcus Sore Throat	21	1	3	1	1	6	14	9	5
Tetanus	—	—	—	—	—	1	1	—	—
Trachoma	—	—	—	—	—	1	—	—	—
Trichinosis	1	—	—	—	—	—	—	—	—
Tuberculosis (Pul.)	22	22	46	40	31	34	25	41	34
Tuberculosis (O. F.)	6	—	6	—	3	1	1	5	1
Typhoid Fever	5	—	2	3	—	—	1	1	—
Undulant Fever	2	3	1	—	—	2	1	—	—
Whooping Cough	94	102	151	166	77	40	44	46	39
Gonorrhea	34	18	20	15	30	21	16	19	11
Syphilis	90	30	34	29	60	67	47	32	40

Remarks: No cases of Asiatic cholera, glanders, plague or yellow fever during the past seven years.

THE AWARD OF THE LESLIE DANA MEDAL TO DR. JOHN M. WHEELER

Dr. John M. Wheeler, professor of ophthalmology in the Medical School of Columbia University and director of the Eye Institute at the Columbia-Presbyterian Medical Center in New York, was presented with the Leslie Dana Gold Medal for "outstanding achievements in the prevention of blindness and the conservation of vision" at a dinner given in St. Louis, in his honor, on the evening of May 9. Dr. Wheeler was selected for the award by the National Society for the Prevention of Blindness in co-operation with the St. Louis Society for the Blind which offers this highly prized mark of recognition annually.

The inscription on the medal reads: "Skilled Surgeon — Great Teacher — Understanding and Sympathetic Friend."

Dr. Wheeler is a former president of the American Academy of Ophthalmology and Otolaryngology. In addition to his work at the Eye Institute of the Medical Center, he is a consultant at six other large New York hospitals. His most publicized operation was performed in 1931 when he removed a cataract from the left eye of the King of Siam.—*Bulletin*, National Society for the Prevention of Blindness.

CORRESPONDENCE

A SUGGESTED PLAN

May 11, 1936.

Editor, *New England Journal of Medicine,*

One cannot refrain from saying something when one reads in *The New England Journal of Medicine* of May 7, 1936, page 957, under the heading of "Two Worthy Indigent Physicians" a plea, for anyone interested to aid two elderly women physicians.

We physicians are supposed to be educated, worldly and broadminded and expect to be respected. What regard can we expect from the people, if such a situation is called to their attention? Their only answer may be, is it possible that the physicians or the Massachusetts Medical Society has no means to help physicians who may be in need of material assistance due to no fault of theirs?

Every other organization consisting of so-called noncollege graduates with degrees or license, has ways and means of helping its needy members, but we "The Massachusetts Medical Society" have no such ways and means, and an appeal must be made through the columns of *The New England Journal of Medicine* to those *who may be interested in contributing money or food.* We should all be interested to help.

The Massachusetts Medical Society should bow its head in shame. We should have a special fund and each Fellow should be requested to contribute a reasonable sum yearly and such funds should be put away and used to help any Fellow who may be unable to support his family or himself.

We can easily raise funds for such a worthy cause and many of those who are more fortunate than others, may contribute additional sums to the Fund.

Our Annual Meeting is scheduled for June 8, 9 and 10 in Springfield. The Fellows should be interested enough to bring in resolutions whereby such a fund could be established for the use of any Fellow who may need aid.

BERNARD ZUCKERMAN, M.D.
978 Blue Hill Avenue,
Dorchester, Mass.

THE CANVASS OF CHRONIC AND DISABLING ILLNESS*

Treasury Department
Public Health Service
Washington

May 12, 1936.

Secretary, Massachusetts Medical Society,

Dear Dr. Begg:

The field staff of the National Health Survey, carefully trained in gathering detailed, accurate information, has completed the extensive canvass of chronic and disabling illness conducted by the United States Public Health Service in nineteen states.

When the study was initiated last fall, the program was discussed in the October 5 issue of *The Journal of the American Medical Association.* As announced at that time, there was special realization of the great value that would accrue to this scientific survey if supplementary facts could be obtained from physicians in cases of medically attended illnesses. Accordingly, when medical attendance was reported, permission to secure additional data from the doctor was requested of the family by the field worker. Assured that the information would be regarded as confidential and would be used for purposes of statistical compilation only, families were co-operative in granting the privilege of confirming diagnoses.

Appropriate forms are now being received by the attending physicians named by informants, and the Health Survey is asking the co-operation of members of the medical profession in this very important phase of the study. It will be appreciated if you will announce the confirmation plan to your Society, urging the desirability of having the forms returned as promptly as possible.

For each form filled and returned the physician will receive a fee of twenty-five cents, a small compensation for the service he will render in executing the blank. By supplying the information requested he will contribute invaluable data to this study and assure the scientific accuracy of the results.

Very sincerely yours,
L. R. THOMPSON,
Acting Surgeon General.

*In a personal letter to Dr. Begg, Secretary of the Massachusetts Medical Society, Dr. Thompson requests that this letter be read at meetings of the District Medical Societies of which physicians of Boston, Fall River, Greenfield, Ipswich and Pittsfield are members, because the study was conducted in the several cities named.

TO THE MEDICAL PROFESSION OF MASSACHUSETTS

From
L. R. Thompson
Assistant Surgeon General

Within a short while, many physicians will receive from the Surgeon General of the United States Public Health Service a request for information relative to the correctness of the diagnoses as reported by certain of their patients. The information solicited is to be returned by mail directly to the Surgeon General. *It will be treated as strictly confidential and will be used for statistical analysis only.* Thus, the ethical and legal standards of the medical profession are in no way violated.

A sum of $200,000 has been set aside from which to pay twenty-five cents (25¢) for the filling out of each medical report by the physician. Physicians will receive report forms to be filled out in groups of ten or more.

During the past five months, the United States Public Health Service has been conducting a National Health Inventory, which has comprised the collection of data from 800,000 families, representing various economic and social levels of the general population.

The survey was designed primarily to obtain use-

ful statistics upon the incidence of the chronic and disabling illnesses as well as upon the various economic, social, and material factors in the environment which may predispose to such conditions.

The actual collection of factual data from the 800,000 selected families by specially trained lay canvassers has now been brought to a close. Care has been taken to avoid having the lay enumerators collect actual medical information. In every instance, the enumerator has simply asked the householder what diseases have occurred in the household during the past twelve months, and has recorded only the exact words of the informant. Many of the schedules have, of course, recorded no illness at all.

For those family schedules upon which an illness is recorded, the attending physician is also recorded, and the head of the household, housewife, or some member of the household in a position to give such permission, has been asked to grant the Surgeon General permission to confirm the reported illness or illnesses with the attending physician.

It is now planned to obtain additional information as to the recorded illness *from the physician who treated the case.* In all of the 95 cities where the survey is being conducted, the co-operation of the local medical society has been obtained.

The United States Public Health Service, in initiating this survey, has used every precaution to make the study scientifically accurate. It has been conducted on the same lines and in accord with the policies laid down by the Service many years ago. The doctor holds a most important position in supporting the scientific value of the material collected. Therefore, I am taking the liberty of requesting, on behalf of the Service, your active co-operation in securing from those physicians concerned in the actual reporting of cases recorded in the survey and from those interested in collection and dissemination of epidemiological statistics.

SAMPLE SCHEDULE (DIABETES)

Serial No. .....
Survey
City .....

Doctor's Name .....
Address .....
City
State .....

United States Public Health Service

HEALTH SURVEY

CONFIDENTIAL Data will be used for statistical purposes only

Patient's Name .....Person's No. .....
Address .....
Nature of illness as reported by family.....
.....
Is report correct? (Yes or No).....
If report is incorrect, please give your precise or provisional diagnosis.....
.....
Has patient been receiving insulin? (Yes or No).....
Complications (check) Cataract..... Arteriosclerosis.....
Others (Specify).....
.....

H.S. FORM 42F
U.S.P.H.S.
Health Survey

RECENT DEATHS

CURRAN—SIMON FRANCIS CURRAN, M.D., of 104 Norfolk Street, Dorchester, died at his home, May 19, 1936.

Dr. Curran was born in 1874 and graduated from the Tufts College Medical School in 1902. His premedical education was acquired at Tufts College where he was prominent in athletic activities. He served as captain and later as major in the World War and had been President of the St. Vincent de Paul Society at St. Matthew's Church in Dorchester.

Dr. Curran had been in poor health since he was injured by a fall in 1935 and had recently submitted to a surgical operation at the Boston City Hospital. Two brothers, William B. of Winthrop and John J. of Dorchester, and three sisters, Mrs. Katherine Gillis of Dorchester, Mrs. Elizabeth Brown of Lowell, and Miss Gertrude A. Curran of Dorchester, survive him.

JENCKES—JOSEPH FRANKLIN JENCKES, M.D., of Wrentham, Massachusetts, died at the home of his son in Providence, R. I., May 18, 1936. Dr. Jenckes was born in 1848, the son of Joseph Smith Jenckes and Harriet Bismore Jenckes of New Bedford.

His medical degree was conferred by the University of Vermont College of Medicine in 1882. He practiced in Wrentham for more than fifty years.

Dr. Jenckes was Chairman of the Board of Trustees of the Fiske Public Library from 1892 until his death and had served on the Wrentham School Committee and Board of Health. Dr. Jenckes was an Odd Fellow, a Mason, and a member of the Thurber Medical Association.

HASKINS—FRANK EUGENE HASKINS, M.D., of 204 Huntington Avenue, Boston, died at his home May 24, 1936, after a long illness. He was born in 1874.

Before studying medicine Dr. Haskins was a graduate of the Massachusetts College of Pharmacy. He later entered the Tufts College Medical School and graduated therefrom in 1903, later becoming Professor of Pharmacology and had also served as Secretary of the Medical and Dental School Faculty.

He was a Fellow of the Massachusetts Medical Society and the American Medical Association and several other medical organizations.

NOTICE

LAWRENCE J. MCCARTHY, M.D., announces the removal of his office to 524 Commonwealth Avenue, Boston. Telephone Kenmore 0600.

REPORTS OF MEETINGS

HARVARD MEDICAL SOCIETY

The stated meeting of the Harvard Medical Society was held in the amphitheatre of the Peter Bent Brigham Hospital on Tuesday evening, April 14, at 8:15 P.M. Dr. David Cheever presided.

Medical and surgical cases were first presented. The first patient, shown by Dr. A. G. Friend, was a twenty-eight year old woman who entered the hospital with the chief complaints of fatigue and moderate diarrhea. In December, 1932, the patient had been operated on for a fistula in ano, and the sinus tract had been shown to be tuberculous on pathological examination. Past history and family history were not otherwise remarkable. The patient entered again in April, 1934, with a story of gradually increasing diarrhea, weakness and fatigue. There was marked pallor, and the hemoglobin had fallen to 25 per cent and the red blood count to 2,000,000. The patient responded well to iron and hydrochloric acid (there was an achylia gastrica) therapy, and at discharge the hemoglobin had risen to 52 per cent and the red count to 3,000,000. Four months before the present admission, the patient ran out of iron and failed to continue to take it. Three months before re-entry, weakness, vague periumbilical pain, and loose bloody stools had their insidious onset. The patient was readmitted with a hemoglobin of 35 per cent and red count of 2,000,000. She has again responded well to increased iron, hydrochloric acid, and protein intakes. The presumptive diagnosis is chlorosis. In discussing the case, Dr. C. Sidney Burwell mentioned the fact that chlorosis is a vanishing disease and drew attention to the similarity between it and the "primary hypochromic anemia" of adults. There was no evidence of disseminated tuberculosis in this patient.

A fifty year old Negro housewife was presented by Dr. Anderson of the Surgical Service. The patient had entered the hospital on April 7 with chief complaints of itching skin and a gradually enlarging abdomen. Family history and past history did not seem relevant. The menopause had come five months before entry. There was no history of indulgence in alcohol. On entry there was a definite icteric tint to the sclerae, and a nonspecific maculo-papulopustular skin eruption. The heart, lungs, and extremities were not remarkable. The abdomen was greatly enlarged and with flatness in the flanks and shifting dullness. No masses were palpable. The blood counts were essentially normal, the icteric index was 40, the nonprotein nitrogen of the blood 24 mg. per cent, and the Wassermann reaction was negative. Two days after entry the abdomen was tapped and five liters of fluid removed. Examination of the fluid showed a specific gravity of 1.010 and a cell count of 150 white blood cells per cubic millimeter, with 90 per cent mononuclear forms. No masses were palpable after the paracentesis. The diagnosis was cirrhosis of the liver with ascites. Various palliative procedures were discussed and exploration was advised.

The chief speaker of the evening was Dr. Reginald Fitz, who had chosen "Medical Inheritance" for his subject. Dr. Fitz presented a very interesting discussion of many ramifications of the subject, graphically illustrated with lantern slides. Of eight hundred men admitted to the Harvard Medical School 20 per cent were sons of doctors. This group of young doctors stood abnormally high in the mental aptitude tests given in medical school, although in actual school-grades such a situation did not obtain. Thirty-three per cent of 1725 doctors queried by Dr. Fitz showed a familial tendency toward medicine as a profession. Doctors listed in "Who's Who" had a 45 per cent family inheritance. Professors in medical schools showed a similar percentage, whereas the so-called "ordinary graduates" showed a 20 per cent "inheritance". The speaker went on to discuss other aspects of "inheritance" in medicine considered in a general way. Whereas 4500 persons enter the "melting pot" of medicine each year, only 2600 leave by death. Thirty-eight per cent of our doctors fall in the age group of twenty-five to forty-four, 50 per cent forty-five to sixty-four, and 12 per cent over sixty-five years of age. Since 1790, the membership in the Massachusetts Medical Society has increased about proportionally to the increase in population, but the actual increase of doctors in Massachusetts has been much greater. Dr. Fitz traced cursorily the profound effects on the practice of medicine and the doctor's social inheritance induced by the development of the telephone, the automobile, electricity, and the influence of the Civil War, the Spanish War, and the World War. He raised the question of whether lay people should have some control over the general regulation of medicine as well as doctors, and personally thinks they should. He traced the development of the State Board of Health and State production of vaccines after the turn of the last century, and mentioned the lessons in efficiency and organization that have been learned from the World War. He showed graphic charts of the influence of the depression on hospital and medical incomes and budgets, and mentioned the great increase in interest of the medical world in socioeconomic problems, as the future and fortunes of medicine become indissolubly linked with the prosperity of the country as a whole. Dr. Fitz cannot help but feel that medicine is on the "State Road." Dr. Burwell emphasized the modern trends in the way of organization taking place, in discussing the paper, and Dr. T. B. Quigley told briefly of the "middle way" Sweden has taken along the path of socialization.

FAULKNER HOSPITAL CLINICAL MEETING

The last clinical meeting for the current year was held at The Faulkner Hospital on Thursday afternoon, May 7, at 5:00 P.M.

Two interesting cases of jaundice which had come to autopsy during the past month were discussed. The first case was one of a fifty-six year old woman, who had had one attack of pain followed by jaundice with subsidence of all symptoms a few months before the present illness. The present illness started with epigastric pain and jaundice. When the jaundice developed, the pain subsided. The jaundice persisted. There was no evidence of bile in the stools. It was felt that there was a stone in the common duct which was verified at operation. Without apparent cause clinically or at autopsy, following the operation the patient went into collapse and died. The lesson to be learned from this case is the importance of operating on gallstones which are giving symptoms at a time when the patient is not jaundiced or the gallbladder acutely inflamed. Had this patient been operated on in the period between the two attacks when she was not jaundiced, the result might have been different.

The other case was one of painless jaundice which had persisted for three and a half months. During the early stages of the jaundice, no observation had been made as to the character of the stools. When the patient was admitted to the hospital there was intense jaundice with marked excoriations of the skin due to intense itching. The stools were clay-colored. The physical examination, except for a palpable liver in the epigastrium, was essentially negative. It was felt that exploration was indicated on the chance that there might be a silent stone in the common duct. It was also hoped that the gallbladder could be anastomosed to the intestine if an obstruction was found at the lower end of the common duct, thus relieving the distressing symptom of itching. At exploration a small common duct and a small gallbladder were found showing that there was no obstruction. A probe passed up toward the hepatic ducts easily penetrated into the liver. Just what caused the intense jaundice with absence of bile entering the intestine was not made clear at operation, and it was felt that there must be serious damage to the liver in the nature of a hepatitis, although the absence of bile in the intestines would be unusual in such a condition. Following the operation, there was considerable hemorrhage which was controlled by placental extract by mouth and thromboplastin inserted into the wound on gauze. Again the actual cause of the patient's death was not established clinically or at autopsy, but was felt to be associated with the intense jaundice. At autopsy a carcinoma originating from the bile passages in the neighborhood of the hepatic ducts was found, which had become extensive enough to occlude both hepatic ducts. At operation the probe passed up toward the hepatic ducts and had gone through this pliable tissue without any obstruction. This location for a primary carcinoma is exceedingly unusual, and although this case does not in any way contraindicate exploration as a diagnostic procedure, it warns one to be careful about making a promise of relieving itching with an anastomosis between the gallbladder and the intestines.

Following the presentation of these two cases, Dr. John S. Hodgson gave a very interesting and instructive talk in regard to some of the points which practitioners should bear in mind when meeting with cases of head injuries which are so common in these days of automobile accidents.

He called attention to the fact that twenty years ago there was too much operating on cerebral accidents and fifteen years ago the pendulum had swung the other way, and there was perhaps too much conservatism. The important point is to realize the possible types of injury and appreciate which ones are benefited by operation, which by repeated lumbar puncture, and which by expectant treatment.

He emphasized the importance of treating the shock which often accompanies these cases and made it clear that there was no hurry in determining by x-ray examination whether the skull was fractured, because pressure within the skull rather than the actual break in the bones is the important point in most cases.

In instances where there is suspected bleeding from the middle meningeal arteries, it is of interest to know whether the break is in that region, and also, in certain cases of depressed fracture of the skull, an x-ray is helpful.

He emphasized the importance of palpation of the scalp, especially of the bone underlying a break in the skin and warned against confusion between depression in a hematoma of the scalp and depression in the bones of the skull.

He believes in scrupulously cleaning up a scalp wound associated with trauma so that it can be sewed up tight. The history of the case is always important, especially in regard to the onset of unconsciousness, whether it occurs instantly or develops gradually.

He also emphasized the importance of frequent, careful neurological examinations in order to detect changes in reflexes and muscle weaknesses.

He emphasized the importance of the slow and bounding pulse, and of stertorous or irregular or slow respiration. Rising temperature is a bad sign and a steadily rising blood pressure is a bad prognostic sign, but in some cases the blood pressure is very little affected. Lumbar puncture in these cases is of considerable diagnostic value and may be of help in treatment. Dr. Hodgson does not have the fear, expressed by some, of the dangers of lumbar puncture if it is carefully done and attention paid to the amount of fluid withdrawn.

If the lesion in the brain is due to a subarachnoid hemorrhage, the spinal fluid will show blood and these cases can be cleared up often by lumbar punctures, repeated often enough to control the intracranial pressure.

If it is an extradural hemorrhage due to a tear in the middle meningeal arteries a lumbar puncture

will probably not show blood unless the dura is torn also, and these cases must be treated surgically.

The most subtle of the head injuries is the subdural hematoma which is usually over the cortex but may be located at the base. The lumbar puncture in these cases may or may not show blood in the spinal fluid, and if there is blood at the start, it may gradually disappear as these hematomas tend to wall off. The clinical course in these cases is often of valuable aid, for the patients show gradual improvement for a few days and then the condition becomes stationary or the signs and symptoms become more pronounced and positive evidence may or may not be picked up on neurological examination. In these cases, operation is the proper procedure.

He called attention to the cases of concussion and cases of contusion with local or general edema, some of which may even have laceration of the brain. These cases usually clear up simply by expectant treatment.

There will be no clinical meetings at The Faulkner Hospital during the summer months, but these meetings will begin again in October.

MASSACHUSETTS GENERAL HOSPITAL CLINICAL MEETING

A clinical meeting of the staff of the Massachusetts General Hospital was held on the evening of March 26, 1936, Dr. Marshall K. Bartlett presiding.

Dr. John Hodgson presented the first paper of the evening on "Lyndau's Disease." This term was first used in 1926 when Lyndau described a group of cases with multiple congenital blood vessel tumors, which are especially apt to involve the retinae and cerebellum. There have been no authentic cases effecting the brain above the tentorium. These congenital abnormalities arise from the mesoderm and are laid down in the third fetal month. The blood vessel abnormalities vary from the capillary to the cavernous type and are most commonly solitary, though they may be multiple and occasionally occur in the spinal cord. Pathologically the lesions in the central nervous system are classified as hemangioblastoma and tend to form cysts from the exudation of plasma. The cyst walls are formed of glial tissue. In 20 per cent of the cases reported, more than one member of the family has the condition. The diagnosis is usually made on the discovery of an enlarged artery and vein which proceeds from the central disc to the periphery of the retinae and into a rounded tumor which may be raised several diopters. Dr. Hodgson stressed the necessity of careful ophthalmologic examination, because these lesions may be small and are usually in the periphery. They may later cause glaucoma or separation of the retina. The clinical picture is of a progressive diminution of vision and sometimes pain and cerebellar symptoms. Any of these symptoms may appear first. The eye lesions usually require enucleation, and the cerebellar tumor may at times be completely removed, because they are usually small and near the surface of the brain. When it is impossible to remove them, x-radiation is of definite benefit. At times there is also a coexistence of this condition with cystic disease of the pancreas and kidneys. The condition is slightly more prevalent in males and a history of injury is frequent. There have been three proved cases at the Massachusetts General Hospital and a fourth probable one.

Dr. Hodgson related the history of these cases, all were males and varied from twenty to forty-five years of age. The cysts were drained in three cases with marked improvement following, but in none could the tumor be entirely excised. In the fourth one, no tumor could be found until postmortem, although a cyst was found in the left cerebellum. Slides were shown of the retinal tumors and of the cerebellum. One of these cases was the first ever to be diagnosed antemortem. Dr. Viets discussed the condition briefly and stressed the importance of wide dilatation of the eyes and a careful ophthalmologic examination.

The second paper was by Dr. W. J. Mixter on the "Operative Treatment of Syringomyelia." A patient was shown with this condition, who, ten years ago, had had scoliosis and recently noted weakness and atrophy of the muscles of the right hand and question of some atrophy of the left hand. There was tingling of the extremities, dizziness and headaches. Examination showed a loss of temperature sensation over the right shoulder and some spasticity in both legs. The spinal fluid was negative. The patient was operated on, the cervical cord exposed, found to be enlarged with a cystic cavity within its substance. This cyst was opened in the midline and the inner lining sutured firmly to the arachnoid. The patient is improving rather slowly, but definitely.

These cases frequently have scoliosis and the spinal canal in the cervical region is usually greatly enlarged, as shown by x-ray. The cavity is lined with a smooth membrane which is easily sutured to the arachnoid. Five cases have been treated in the above manner. All had scoliosis and all had cavities in the cervical cord. Three of these have shown improvement and there is hope of greater success in the future when the condition is recognized at an earlier date. Dr. Mixter stressed the fact that all cases of existing scoliosis should have careful examination of the cervical spine, both by x-ray examination and neurological studies.

The third paper was presented by Dr. J. C. White on "Blood Loss in Cranial Operations." Dr. White contrasted neurosurgery and general surgery as to the increased importance of hemostasis in the former type, also a proper fluid balance is more important because of the danger of cerebral edema. He described, briefly, an efficient method of determining the blood loss in any operation. All of the hemoglobin is carefully washed from the drapes and all the blood saved. The amount of hemoglobin is determined, and from it the total blood loss calculated. It was found that in the excision of a meningioma, there is usually a loss of about 2000 cc. of blood. In

a bone flap for exploration, 500 to 1500 cc. is lost and in a laminectomy 300 cc. This blood loss has been greatly reduced by the use of adrenalin.

Besides the loss of blood, at operation, there is a great deal of fluid also lost from both sensible and insensible perspiration and from the lungs. In general, a neurological operation results in less sweating than in general operations because there is less sympathetic stimulation. Several cases were studied in detail as to the fluid balance and it was found that a postoperative patient with a temperature of 101 degrees, lost one liter of fluid by insensible perspiration per day. If the temperature was 103 degrees, two liters were lost. A normal person lying in bed loses about 700 cc. in this way. In preventing loss of fluid during operation, straight ether is not a good anesthetic because it dilates the brain vessels, nor is nitrous oxide and oxygen because here the blood pressure is raised. The ideal anesthetic is avertin (about 90 mg. per kilogram of body weight), followed by novocain and adrenalin locally. Luminal is a good preoperative medication. Dr. White has found that the use of adrenalin diminishes the loss of blood by twenty-five per cent in turning down a bone flap. He said that about 300 to 500 cc. is lost in turning down a bone flap under these conditions and for the removal of an avascular tumor there is some 200 to 500 cc. additional loss. In a vascular tumor 1000 to 1500 additional loss of fluid takes place. For the replacement of blood loss he recommended: (1) If the blood loss is 500 cc. or less, the patient should be given 2000 cc. of intravenous saline. (2) If the blood loss amounts to 1000 cc. the patient should be transfused postoperatively and receive 2000 cc. of saline intravenously. (3) If the blood loss is 1200 cc. or above, there should be a saline intravenous and multiple transfusions going on during the operation. The patient can take what he needs by mouth usually after the first twenty-four hours. A careful calculation of the intake and output is essential. An excessive fluid intake may do a great deal of damage by causing cerebellar edema. If the patient's kidneys are normal, he can excrete the normal nitrogenous materials in 500 cc. of urine, but if he can only concentrate his urine to 1.010, he needs to excrete 1500 cc. in a day. A house diet contains about 1000 cc. of fluid, whereas a soft-solid diet contains 500 cc., and the water of oxidization from the food intake is about 250 cc.

Dr. Reginald Smithwick spoke on "Hypertension." It has been found in the study of essential hypertension that no treatment, thus far described, materially influences the course of the disease. It occurs in a wide age range, occasionally coming in the second decade of life and occurring with increasing frequency after this. In the early stages, the blood pressure is variable and frequently normal. But as the disease progresses, the average level rises to a high figure and never becomes normal. The pathological changes that occur are arteriolar and are most marked in the eyes, brain, heart and kidneys. Death in 60 per cent is due to heart failure, in 20 per cent to cerebral accident and in 10 per cent to renal failure. These patients have a high degree of emotional instability and show a blood pressure rise in response to change of temperature. If the hands of one of these patients are dipped in ice water for a few minutes, there will be a marked rise in blood pressure. Sympathectomy at times has been shown to offer relief in a carefully selected group of cases. The several operations which are possible to cut the sympathetic fibers in their course were shown diagrammatically. Following the section of these fibers, the blood vessels become sensitized to circulating hormones, particularly adrenalin, so that the effect of lowering blood pressure is definitely diminished. However, this sensitivity occurs to a much less extent if the preganglionic fibers rather than the postganglionic fibers are sectioned, although this does not completely abolish this sensitivity. If the adrenals are denervated, the effect is greater and the blood vessels react to blood hormones less. The ideal operation accomplishes the sympathectomy of a large blood vessel area, by a simple procedure. Some people have sectioned the anterior roots from the sixth thoracic to the second lumbar vertebra, but this is a dangerous procedure with a high mortality and results in considerable muscular paralysis.

There are several other possible approaches and Dr. Smithwick pointed out that if the adrenal glands are denervated it is not so important to cut the preganglionic rather than the postganglionic fibers. It has been the feeling at the Massachusetts General Hospital that the most logical operation cuts the three splanchnic nerves. When these are cut, the kidneys and adrenals are denervated and these fibers are presumably preganglionic. This operation has had widespread popularity in the past three or four years. At the Massachusetts General Hospital there have been six patients who have had these nerves injected with alcohol and the effects have been slight to striking. Slides were shown on the approach used at the present time at this hospital in which five to six inches of the trunks of the splanchnic nerves are removed. Results from nine cases were reported. Three of the cases were in young people with marked fluctuation of the blood pressure, which at times was normal. These patients were, then, in the early stages of the disease and following operation showed a very definite diminution and a stabilization of the blood pressure with a lowering of the average reading. Three other cases were more advanced with a more striking fluctuation and a blood pressure that was always above normal. In this group there was a material reduction of the blood pressure. In the third group, also, consisting of three cases, the blood pressure was higher, the patients were older and following operation there was no change. Dr. Smithwick summed up his talk by concluding that this was a definitely beneficial procedure in the group of cases in which the disease was in its early stages, but was of practically no benefit in the more advanced ones.

Dr. Palmer spoke briefly on the medical aspect of the disease and pointed out with the exception of age and weight, that in the younger group of individuals the disease is apt to be very intense and rapidly progressive. It occurs more frequently in females and especially if abnormalities of the catamenia are present.

BOSTON SOCIETY OF BIOLOGISTS

A meeting of the Boston Society of Biologists was held on the fifteenth of April in the Harvard Biological Laboratories in Cambridge.

Dorothy R. Gilligan spoke on "The Distribution of Solutes Between Plasma and Body Fluids." Edema fluid, pleural fluid, ascitic fluid, lymph, joint fluid and spinal fluid were studied. The chloride ion is always higher in these liquids than in serum and varies with the protein content of the fluid. Careful calculations were made according to the Donnan theory of equilibrium and then compared with the actual ratios figured on experimental data. Except in the cases of calcium and potassium, these experimental and calculated ratios closely resemble each other. It is known that some of the calcium is bound and probably some of the potassium is also bound; thus accounting for the discrepancy in regard to these two ions. Lymph has almost the same composition as serum fluid except that the potassium content of the former is higher. Amniotic fluid approaches the content of serum in early pregnancy, but becomes hypotonic in the later months, possibly due to the dilution with fetal urine. Synovial fluid has a high protein content and contains mucin but otherwise is similar to edema. In studying cerebrospinal fluid, it was found that this fluid does not correspond well with Donnan's Law of equilibrium and it is therefore felt that it is not a pure dialysate. The bicarbonate and phosphate content of spinal fluid is lower than it would be if it were a simple dialysate. Mrs. Gilligan concluded that subcutaneous fluid, chest fluid, abdominal fluid, synovial fluid, early amniotic fluid, and lymph are simple dialysates in equilibrium with plasma, but that spinal fluid does not fall in the same category.

Dr. Robert E. Johnson spoke on "Funk's Fat Metabolism Hormone." In 1932 a water soluble substance was extracted from urine and when injected into rats, it caused an increase in acetone bodies, sugar, and lactate in the blood. It is extracted by Doisy's method of extracting sex hormone from urine. The "hormone" is relatively unstable and is completely destroyed in twenty-four hours. It has been found that dogs excrete approximately three times as much following hypophysectomy as they did before, and for this reason it is believed that the substance is not excreted by the pituitary gland. There is no difference before and after thyroidectomy in the excretion of this substance. In normal human beings one liter of urine contains about one unit of this "hormone", but if the calculation is made after the patient has exercised while fasting, there are about seven units per liter excreted. To date there has been no conclusive proof that this substance is a true hormone.

Dr. Morgan Upton spoke on "The Time Factor in the Discrimination of Successive Stimuli with Especial Reference to Sound." The so-called "time error" phenomenon has been known for some time. When a second stimulus of the same intensity as the first is heard, it is judged greater or less than the first, depending on the time elapsing between the two stimuli. Doctor Upton has studied this phenomenon and feels that the difference which occurs in the early small intervals of time is representative of some rapidly decaying cortical process and in the longer intervals it is a function of memory. He discussed the various theories that have been promulgated to explain the above effect. Experimentally it is found that if the interval is less than 1.5 seconds, the second stimulus seems greater than the first. The work of other investigators indicates that there is a range between 1.5 seconds and 3 seconds where the second stimulus appears to be smaller than the first, while beyond three seconds the second again appears to be greater.

WORCESTER DISTRICT MEDICAL SOCIETY

At the Annual Meeting of the Worcester District Medical Society on May 13, 1936, the following officers were elected:

President, Roy J. Ward, Worcester; Vice-President, William A. Bryan, Worcester; Secretary, Erwin C. Miller, Worcester; Treasurer, Edward P. Disbrow.

Commissioner of Trials, Walter P. Bowers, Clinton; Censors, Supervisor, George A. Dix, Worcester; Charles N. Church, Millbury; John J. Dumphy, Worcester; Joseph P. Mulhern, Worcester; Bancroft C. Wheeler, Worcester.

Councilors: James C. Austin, Spencer; Walter P. Bowers, Clinton; Leslie R. Bragg, Webster; Philip H. Cook, Worcester; William J. Delahanty, Worcester; George A. Dix, Worcester; Ernest B. Emerson, Rutland; George E. Emery, Worcester; Michael F. Fallon, Worcester; Homer Gage, Worcester; James J. Goodwin, Clinton; David Harrower, Worcester; Ernest L. Hunt, Worcester; Edwin R. Leib, Worcester; William F. Lynch, Worcester; Arthur W. Marsh, Worcester; Erwin C. Miller (Secretary), Worcester; Joseph W. O'Connor, Worcester; Walter C. Seelye, Worcester; Edward R. Trowbridge, Worcester; Roy J. Ward (President), Worcester; Frank H. Washburn, Holden; Royal P. Watkins, Worcester; Samuel B. Woodward, Worcester.

Councilor for Nominating Committee: Principal, David Harrower, Worcester; Alternate, Royal P. Watkins, Worcester.

ERWIN C. MILLER, M.D., *Secretary.*

ESSEX SOUTH DISTRICT MEDICAL SOCIETY

A stated meeting of the Essex South District Medical Society was held at the Salem Country Club, Peabody, Mass., on May 13, 1936.

Following the dinner at 7 P.M., the Annual Meeting was held. The following officers were elected:

President—C. A. Bonner, Hathorne; Vice-President—E. D. Reynolds, Danvers; Secretary — R. E. Stone, Beverly; Treasurer — Andrew Nichols, III, Danvers; Commissioner of Trials—O. C. Blair, Lynn; Censors — A. E. Parkhurst (Supervisor), Beverly; S. N. Gardner, Salem; S. R. Davis, Lynn; J. J. Hickey, Peabody; I. B. Hull, Gloucester; Nominating Councilor — Hanford Carvell, Gloucester; Alternate Nominating—R. E. Foss, Peabody; Councilors—C. F. Deering, Danvers; R. E. Foss, Peabody; J. F. Jordan, Peabody; C. L. Curtis, Salem; N. P. Breed, Lynn; J. W. Trask, Lynn; C. H. Phillips, Beverly; W. G. Phippen, Salem; J. F. Donaldson, Salem; O. S. Pettingill, Middleton; A. E. Parkhurst, Beverly; Hanford Carvell, Gloucester; B. B. Mansfield, Ipswich; J. G. Corcoran, Hamilton; Executive Committee — J. R. Shaughnessy, Salem; R. P. Hallett, Gloucester; C. F. Twomey, Lynn; Sherman Golden, Beverly; O. S. Pettingill, Middleton; E. C. Yerbury, Hathorne. C. A. Bonner and R. E. Stone are also Councilors by reason of their office.

Dr. Paul Dudley White of Boston then gave a very interesting description of his travels to the ancient shrines of medicine in Greece and Italy. Beautiful moving pictures and lantern slides enhanced the charm of his presentation.

NATHANIEL P. BREED, M.D.

THE HARVEY CUSHING SOCIETY

The fifth annual meeting of the Harvey Cushing Society was held in the Mayo Clinic, Rochester, Minnesota, May 15 and 16, 1936. The following officers were elected: Dr. Kenneth G. McKenzie, Toronto, Canada, President; Dr. Richard Meagher, New York City, Vice-President; Dr. Louise Eisenhardt, New Haven, Secretary and Treasurer. Dr. Ernest Sachs, St. Louis, was elected an Honorary Member. Corresponding Members chosen were Dr. Herbert Olivecrona, Stockholm; Dr. Otfrid Foerster, Breslau, and Mr. Hugh Cairns, London.

The morning sessions were devoted to a program by the members of the Mayo Clinic, with presentations of preoperative and postoperative cases, and neurosurgical clinics. Contributions by members of the Society included: notes on the conservative treatment of tumors of the third ventricle, by Dr. Glen Spurling, Louisville; the management of intracranial arteriovenous varices, by Dr. R. E. Semmes, Memphis; trauma of the head, by Dr. Nicholas Gotten, Philadelphia; osteomyelitis of the skull, by Dr. Edgar Fincher; ureterodural anastomoses in hydrocephalus, by Dr. Frederic Schreiber, Detroit; certain peculiarities of the trigeminal nerve, by Dr. Temple Fay, Philadelphia; pneumocephalus following operation upon the sensory root of the fifth nerve, by Dr. W. G. Crutchfield, Richmond, and experimental cerebral edema, by Dr. Cobb Pilcher, Nashville.

A round-table discussion was held on the subject of the surgery of hypertension and peripheral-vascular disease. Mr. Peter Ascroft of London reported results of his studies in the Department of Physiology, Yale School of Medicine, on the treatment of vasospastic states: an experimental analysis in monkeys.

At the annual dinner on Friday evening, Dr. John Fulton described the various activities of the Second International Neurological Congress in London. The presidential address, "The Roentgenologist and the Orchestra Leader," was given by Dr. Merrill Sosman.

The next meeting is to be held in Philadelphia.

THE GLOUCESTER CANCER CLINIC

The Gloucester Cancer Clinic Committee reports its spring clinic conference which was held at the Addison Gilbert Hospital on May 20, 1936. The officiating consultant was Dr. George A. Leland, Jr., visiting surgeon at the Massachusetts General and the Palmer Memorial Hospital, Boston.

There were approximately twenty-five doctors in attendance from Beverly, Manchester, Hamilton, Essex, Rockport, Gloucester.

Number of patients examined	13
Number of new patients	8
Diagnoses on new patients were:	
Cancer of colon	1
Cancer of cervix	2
Question of cancer of stomach	1
Question of early cancer of breast	1
Postoperative cancer, no evidence of malignancy	1
Sebaceous cyst	1

Dr. Leland reviewed the patients examined by him at the clinic in January, 1936, in order that the visiting physicians might know the types of treatment these patients had received and observe the present postoperative results.

Luncheon was served at the close of the clinical conference.

Submitted by,

GLOUCESTER CANCER CLINIC COMMITTEE,
E. E. Cleaves, M.D., *Chairman*,
Scott W. Mooring, M.D.,
Ira B. Hull, M.D.,
William W. Babson, M.D.,
William R. Irving, M.D.,
Harry C. Burrell, M.D.

OFFICERS OF THE MASSACHUSETTS SOCIETY FOR SOCIAL HYGIENE

At the Annual Meeting of the Massachusetts Society for Social Hygiene held April 30, 1936, the following designated officers were elected: Dr. E. Granville Crabtree, president; Mrs. Maida H. Solomon, vice-president; Elizabeth Ross, secretary; Mrs. William Wadsworth, treasurer. Directors for the ensuing year are Dr. Harold L. Leland, Dr. Gaylord W. Anderson, Herbert C. Parsons, Dr. George Gilbert Smith, Dr. Wilson G. Smillie and Mrs. Eva Whiting White elected on the executive committee, and Dr. Anderson, Dr. John J. Carroll, Dean Lucy

Jenkins Franklin, Dr. Homer Gage, Dr. Smith, Dr. Harry C. Solomon, Mrs. George Whiting, Dr. Alfred Worcester, the Rev. Robert P. Barry, Dr. William B. Keeler, Wilford Cook Saeger, Miss Rosanna D. Thorndike, Dr. L. Jackson Smith and Mrs. I. Tucker Burr.

CAPE COD HEALTH BUREAU ASSOCIATION

The spring meeting of the Cape Cod Health Bureau Association was convened in Hyannis on Friday, May 8, Vice-President Howes in the chair. At the business session the routine reports were followed by a vote to devote $250 of the reserve fund to the equipping of the proposed local milk and water laboratory in the Court House in Barnstable. This, with milk inspector George F. Crocker, Jr., in charge, will furnish to the Cape a home laboratory, and avoid the delay and costs now incident to the testing of samples in Boston or in Amherst.

The election of officers to serve for the coming year resulted in the following: President, Mr. I. Grafton Howes of Dennis; Vice-President, Mrs. Jeanette M. White of Sandwich; Secretary-Treasurer, Mr. C. R. Bassett of Yarmouth, and Executive Council, Dr. Richard P. MacKnight of New Bedford, Dr. A. P. Goff of Hyannis, Mr. E. T. Ward of Yarmouth and Dr. J. G. Kelley of Pocasset.

Dr. R. P. MacKnight, State District Health Officer for southeastern Massachusetts, was the principal speaker, discussing various duties of boards of health and emphasizing the need of accurate and complete records. In his work Dr. MacKnight very frequently encounters unfortunate conditions. When a case of diphtheria is reported, for example, it is important for the nurse to know the immunization conditions of possible contacts, and the absence of records makes her work uncertain and difficult. A mere notebook record is really not sufficient, there should be card records, kept up-to-date, and records of those not immunized should be included.

The same is true of tuberculosis, for the nurse looks at once through the family and other contacts. In populations which include many foreigners, and this is characteristic of a good many towns and cities in southeastern Massachusetts, the problem, if records are not available, becomes difficult.

Incidentally, the speaker noted that good records have their effect on the incidence of some diseases, since the authorities can employ preventive measures, and as in Falmouth, which has had no case of diphtheria in three years, be reasonably assured of improved health conditions.

In scarlet fever, attention should be given to the milk supply, with inquiries as to its distribution and care, and health conditions of milkers and the stables, whether clean or dirty. These items should be of record in form available for consultation. The pasteurization of milk is an effective precaution.

Dr. MacKnight next discussed venereal diseases, one of the important problems in this section, due in part to the character of its population, and the secrecy incident to the disease. Health departments might declare individual cases to be dangerous to the community, but the evidence is very difficult to obtain and the law limits the use of this information when it is obtained.

In closing, Dr. MacKnight stated it to be his opinion that measles ought to be better controlled. With typhoid fever, examinations have increased the number of known carriers, and these can be controlled.

The round-table discussion that customarily follows the papers read at these meetings was devoted largely to various aspects of the venereal disease problems.

Mr. J. L. Glennon, chairman of the New Bedford Board of Health, spoke of the milk control in his city, noting that in 1923, 700 babies died in the first year of life, while in 1935, the figure was only 97. Mr. W. G. Kirschbaum, of the same board, stated that there are only two houses placarded for communicable diseases today in his city, with a population of 110,000. New Bedford has, for twenty-nine months, been without a death from diphtheria. Dr. J. G. Kelley, superintendent of the hospital at Pocasset, said that his institution is conducting a clinic for venereal diseases. Two babies that under former conditions would have had congenital syphilis had been born free from the disease. The clinic is as yet only an experiment.

WILLIAM HARVEY SOCIETY

The April meeting of the William Harvey Society was held on April 10 in the Beth Israel Hospital, Boston.

Dr. Elliott C. Cutler spoke on "War Surgery." He began his talk by pointing out the better side of war and discussed the mechanism by which capable men are advanced much more rapidly than could occur in civil life, while the less capable ones quickly find their place in a corresponding position on the military scale. Dr. Cutler gave a very interesting and highly entertaining account of some of his numerous experiences at or near the front during the World War. He amply illustrated his speech with maps and lantern slides. He took his material from three large volumes of papers that he collected and wrote during the trying years of the war. This often meant spending thirty minutes' writing, out of the five hours that was allowed for sleep. All of the experiences that he recounted from the occasion when the hospital was bombed to the organization of an evacuation hospital, which had to dispose of a thousand wounded daily, were told in Dr. Cutler's fascinating manner and contributed to a thoroughly enjoyable evening.

THE FRANKLIN COUNTY PUBLIC HEALTH ASSOCIATION

Miss Elsie F. Smith, Executive Secretary of the Franklin County Public Health Association, reported at the annual meeting of the Association held in Greenfield, Massachusetts, April 1936, that during 1920 thirty-five persons died of tuberculosis, whereas in 1934 only ten deaths from this disease were

recorded. The number of cases of tuberculosis has declined from 630 in 1920 to an average of 147 pulmonary cases in the past five-year period and 81 childhood cases.

The Treasurer reported a satisfactory financial condition of the Association. Dr. John B. Hawes, 2d, of Boston, gave an inspiring address, explaining that there are three fundamental functions which should be actively in operation in the fight against tuberculosis. These are education, demonstration of existing conditions and intelligent research directed against the etiologic factors underlying the incidence of tuberculosis in any community. He especially emphasized the importance of follow-up work in dealing with contact cases as well as those with a demonstrative infection.

The meeting was presided over by Dr. Charles Moline. The officers elected for the ensuing year are the following: President, Dr. Charles Moline; First Vice-President, Mrs. H. R. Sargent; Second Vice-President, Mr. W. Herbert Nichols; Secretary, Mrs. A. L. Johnson; Treasurer, Mr. Herbert V. Erickson. Mr. Marvin E. Janes and Mrs. Raymond L. Dunnell were elected to the Board of Directors for three years. Miss E. F. Smith was reappointed Executive Secretary.

SOCIETY MEETINGS, CONGRESSES AND CONFERENCES

CALENDAR OF BOSTON DISTRICT FOR THE WEEK BEGINNING MONDAY, JUNE 1, 1936

Tuesday, June 2—

9:30 A.M. Massachusetts General Hospital. Thoracic Clinic.

Wednesday, June 3—

8 A.M. Massachusetts General Hospital. Orthopedic Grand Rounds.

†12 M. Clinico-Pathological Conference. Children's Hospital.

Thursday, June 4—

8 A.M. Massachusetts General Hospital. Circulatory Clinic.

*8:30-9:30 A.M. Clinic, Surgical and Orthopedic Staffs of the Children's Hospital, at the Children's Hospital.

9:15 A.M. Massachusetts General Hospital. Neurological Conference.

12 M. Massachusetts General Hospital. Clinico-Pathological Conference.

Friday, June 5—

10:30 A.M. Massachusetts General Hospital. Fracture Clinic.

Saturday, June 6—

*10 A.M. - 12 M. Staff Rounds at the Peter Bent Brigham Hospital. Conducted by Dr. Henry A. Christian.

*Open to the medical profession.
†Open to Fellows of the Massachusetts Medical Society.

May 28—New England Obstetrical and Gynecological Society will meet at Providence, R. I.

May 28—Clover Hill Hospital, Medical Lecture. 161 Berkeley Street, Lawrence, at 9 P.M.

May 28—Brockton Medical Society will meet at the Commercial Club, Brockton, at 7:30 P.M.

May 31 - June 1—International Cardiological Meeting, Royat (Auvergne) Assembly of Physiologists, Pathologists and Therapeutists. See page 754, issue of April 9.

June 2—Lawrence Cancer Clinic, Lawrence General Hospital, 1 Garden Street, at 10 A.M.

June 4, 5, and 6—Annual Meeting of the American Dermatological Association at the New Ocean House, Swampscott.

June 4 - July 3—Massachusetts Institute of Technology Department of Biology and Public Health. See page 1012, issue of May 14.

June 8—Tufts Medical Alumni Luncheon. See page 1047, issue of May 21.

June 8, 9, and 10—American Association for the Study of Goiter. See page 1075, issue of May 21.

June 9—New England Alumni. See page 1047, issue of May 21.

June 9—Massachusetts Medico-Legal Society. See page 1047, issue of May 21.

June 9—Massachusetts Diplomates of the National Board of Medical Examiners. See page 1047, issue of May 21.

June 15-19—The Executive Board of the Catholic Hospital Association will meet at the Fifth Regiment Armory, Baltimore, Md.

June 16 - July 28—Summer Course in Bacteriology. See page 385, issue of February 20.

June 22 and 23—The Medical Library Association. See page 1075, issue of May 21.

June 29 - July 11—Hospital Administration. See page 957, issue of May 7.

September, 1936—First International Congress of Sanatoria and Private Nursing Homes. See page 803, issue of April 16.

September 7-10—International Union against Tuberculosis. See page 554, issue of March 12.

September 29 - October 3—First International Conference on Fever Therapy. See page 1325, issue of December 26, 1935, and page 1075, issue of May 21.

October 12-18—Third International Congress on Malaria. See page 1076, issue of May 21.

October 19-23—Clinical Congress of the American College of Surgeons. See page 180, issue of January 23.

April 21-24, 1937—American Society for Experimental Pathology. See page 1075, issue of May 21.

BOOK REVIEWS

Consultations de Cardiologie. Georges Marchal. 227 pp. Paris: Masson et Cie. 25 fr.

This small volume of some two hundred pages presents in an interesting way by case histories and discussion the clinical points of view concerning diagnosis and treatment of one group of the French cardiological school, namely, that under Charles Laubry. There are thirty chapters, mostly short, of a few pages each, discussing the following subjects:

1. The evolution of mitral stenosis.
2. The rheumatic origin of aortic insufficiency.
3. The evolution of cardiac rheumatism with heart failure and enlarged liver.
4. Rheumatic pancarditis.
5. Disappearance of signs of valvular defect in a case of acute articular rheumatism.
6. Subacute streptococcus endocarditis.
7. Syphilitic aortitis with left ventricular insufficiency.
8. Neurocirculatory asthenia, with an erroneous diagnosis of aortitis.
9. Syphilitic myocarditis with latent aortitis.
10. Juvenile aortitis due to congenital syphilis.
11. Aneurysm of the arch of the aorta.
12. Senile heart with stationary sclerotic valvular lesions.
13. Senile heart with left ventricular insufficiency.
14. Appearance of ulcer of the stomach due to cardiac insufficiency.
15. Myocardial infarct.
16. A case of extrasystoles.
17. Nodal paroxysmal tachycardia.
18. Syndrome of Adams Stokes, with total bradycardia.

19. Syndrome of Adams Stokes, with complete dissociation.
20. Syndrome of Adams Stokes, with mixed bradycardia.
21. Syphilitic pulmonary arteritis with right ventricular insufficiency.
22. Maladie bleue, with polycythemia.
23. Cardiac neurosis of the menopause.
24. Aerophagia masked as angina pectoris.
25. Malignant arterial hypertension with aortic insufficiency.
26. Complete arrhythmia with cardiac insufficiency in thyrotoxicosis.
27. Case of "curable" myocardial infarct.
28. Grippe with cardiopulmonary symptoms.
29. Severe cardiac insufficiency in a case of filariasis cured by x-ray therapy of the spleen.
30. Cardiac insufficiency in the course of pernicious anemia.

There is a preface by Professor Laubry.

The "consultations" are entertainingly written, and contain many points of interest and value, for example, (1) the comments about the erroneous diagnosis of aortitis with dilatation of the aorta made on x-ray study in a patient who had had syphilis at one time, but at the time of the examination only neurocirculatory asthenia (Case 8), (2) the recognition of the prolonged activity of the rheumatic infection, and (3) the insistence on rations of rest in the treatment of heart weakness.

There are a good many points in the discussion of the cases with which most of us on this side of the water would not agree, for example, in Case 1 the likelihood of a presystolic murmur in the presence of auricular fibrillation, aortic regurgitation produced by the displacement of the aortic cusp by a sclerosed mitral valve, the combined use of digitalis and ouabain, the routine use of much salicylate therapy in rheumatic cases, the use of iodine and sulphur in cardiovascular disease, the possibility of valvular disease subsiding with a disappearance of the murmurs instead of the more rational explanation of the causation of the murmurs in dilatation of the heart, and the failure to treat thyrotoxicosis with cardiac involvement by subtotal thyroidectomy. In general one is unfavorably impressed by the polypharmacy.

One suggestion of particular interest that comes from several of the chapters is the plan of giving prophylactic antistreptococcus injections in cases of valvular disease to prevent the complication of subacute bacterial endocarditis. On page 47 there is a statement that one case of secondary streptococcus endocarditis did develop despite the use of regular injections of vaccine in a number of cases over a period of four years. However, it is to be remembered that only about one case of twenty-five or more of rheumatic valvular disease develops subacute bacterial endocarditis anyway. Nevertheless the subject is an interesting one, and the procedure may possibly be of value.

For a survey of many of the views of the French cardiologists this volume can be recommended, but it must be read very critically.

The Treatment of Diabetes Mellitus. Elliott P. Joslin. 620 pp. Philadelphia: Lea & Febiger. $6.00.

In 1814, was published the first edition of Dr. Jacob Bigelow's famous "Florula Bostoniensis." With characteristic modesty of the time he remarked of this book, "I flatter myself that among its faults, the most numerous will not be its errors; and whatever may be its fate with the public, I shall retain the consciousness that it has not been the result of superficial inquiry or negligent observation."

Dr. Joslin's "Treatment of Diabetes Mellitus" has come to be regarded by all New Englanders as one of the most distinguished of Boston's perennials. Appearing for the first time in 1916, subsequent plantings have budded forth in 1917, 1923, 1928 and 1935, each one breeding true to form and demonstrating to the medical world everything that is worth knowing about Lathyrus odoratus.

The 1935 specimen is much like its predecessors. It has been developed primarily, as were the earlier ones, to record for others those facts which have proved of particular service to Dr. Joslin in the treatment of diabetes. The knowledge of this disease has grown rapidly. All that Dr. Joslin knew of the treatment of diabetes in 1916 could be encompassed in 440 pages; twelve years later, a book of 998 pages was necessary to yield the information which he regarded as essential. The latest volume has been shortened perceptibly without, however, losing anything vital from its contents; and yet, at the same time, it has been broadened to include new knowledge regarding the pathologic physiology of diabetes which has come to light in recent days. As usual, this edition is a fine piece of bookmanship.

Dr. Joslin's textbook is a difficult one to characterize. Certainly, to copy Dr. Bigelow's post-revolutionary restraint, one can at least say of it without fear of contradiction that among its faults the most numerous are not its errors and that the book has not been the result of superficial inquiry or negligent observation. One can even go farther and agree with the more expansive *Boston Medical and Surgical Journal* of the Great War (176: 577 [April 19] 1917), "There is nothing the internist or general practitioner might want to know concerning the treatment of diabetes that is not presented in this admirable book. It is indeed rare that one is privileged to recommend so whole-heartedly such a book to the medical profession." Or perhaps, as a final word, one should act one's age. What the post-war *New England Journal of Medicine* (200: 1012-1014 [May 9] 1929) said a few years ago had best be repeated: "Boston must not fail to acclaim the appearance of a new edition of Dr. Joslin's famous textbook. Any survey of this most important work is inadequate. A study of the book itself will more than repay any reader."